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SPECIAL LISTING

CURRENT CANCER RESEARCH

on

CANCER PATIENT SUPPORTIVE CARE AND PAIN MANAGEMENT

APRIL 1981

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Dear Cancer Researcher:

This **SPECIAL LISTING** of Current Cancer Research Projects is a publication of the INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) Program of the National Cancer Institute. Each **LISTING** contains descriptions of ongoing projects in one selected cancer research area. Approximately 50 different cancer research areas are covered by a separate **SPECIAL LISTING.**

The present series of **SPECIAL LISTINGS** is a third edition, and begins with number 201. This series will update the second edition which included **SPECIAL LISTINGS** numbered 101 through 147. Depending on the total number and types of cancer research summaries received, the third edition will have at least 47 titles, and possibly a few more. In most cases, each third edition **SPECIAL LISTING** will replace the exact subject area of a second edition **LISTING** (SL 201 replacing SL 101, etc.). Whenever the number and variety of summaries requires a change in this procedure, a notation will be made in the specific **LISTINGS** affected.

The purpose of these **LISTINGS** is to promote and facilitate the exchange of information among cancer scientists. The project descriptions in the **LISTINGS** are provided by cancer scientists from more than 50 different countries. Researchers are urged to prepare accurate summaries which will be rapidly processed for inclusion in the CANCERPROJ data base as well as future **SPECIAL LISTINGS.**

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CURRENT CANCER RESEARCH

I. INFECTIOUS DISEASE IN CANCER PATIENTS

A. SURVEILLANCE FOR INFECTIOUS ORGANISMS IN HOSPITALS AND CANCER PATIENTS

1. PREVENTION OF INFECTIONS IN PATIENTS WITH CANCER

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Infection remains as a major cause of both morbidity and mortality for patients with various types of cancers. The risk of infection increases as greater numbers of patients are treated with more intensive cytotoxic and immunosuppressive therapy. It is therefore essential in the modern practice of oncology that definitive approaches be designed and evaluated to reduce the opportunities for infection. At the Baltimore Cancer Research Program an intensive infection surveillance program assesses the ongoing infectious disease status of the patients and the status of the Program as a whole. From this data base have grown appropriate basic infection control policies and specific research approaches including evaluation of laminar air flow rooms, simpler means of air filtration and reverse isolation, oral nonabsorbable antibiotics and techniques to prevent axillary and oral infections. Trimethoprim/sulfamethoxazole, an absorbable antibiotic, is being evaluated as a means of suppressing the aerobic gram-negative flora while preserving colonization resistance. These programs are enforced by the infection control nurse.

BIBLIOGRAPHIC REFERENCES: Schimpff, S.C.: Infection prevention during granulocytopenia. In Remington, J.S. and Swartz, M.N. (Eds.): Current Clinical Topics in Infectious Diseases 1980. New York, McGraw-Hill Book Company, 1980, pp. 85-106. Wade, J.C. and Schimpff, S.C.: Infections in patients with suppressed cellular immunity. In Klastersky, J. and Staquet, M. (Eds.): Supportive Care in Cancer Patients. II. New York, Raven Press, 1980 (in press).

2. SEPSIS IN CANCER SURGERY - BACTEROIDES PATHOGENESIS

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Bacteroides are now recognized as major pathogens in various infections, especially in those consequent to bowel surgery which is frequently, if not primarily, due to cancer of the colon. These bacteria cause extensive tissue destruction and considerable mortality in such cases. Yet, little is known of their mechanisms of pathogenesis or of what converts quiescent intestinal commensals to destructive invaders. We have now isolated and partialy characterized two different endotoxin-like lipopolysaccharides from most species of this genus which we plan to further characterize chemically, biologically and as to their possible involvement in pathogenesis. We will - in this context - study what influence anaerobic growth conditions may exert on the chemical nature of such substances which are similar to but subtly distinct from endotoxins familiar in 'aerobic' bacteria. We will pursue our fortuitous observation that we may be able to greatly speed up diagnosis of Bacteroides infections by either or both of two methods - detection of characteristic enzymes in aspirates from surgical sites before clinical signs are evident, and/or pyrolysis-GLC of cells from colonies on initial isolation plates. Lastly, we will more closely examine B. melaninogenicus with respect to its curious enzymatic disparity as compared with other members of this genus.

3. STUDY OF BACTEREMIA DURING PERITONEOSCOPY

Fossieck, B. E., Huberman, M., Bunn, P. A., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Medical Oncology Section, *50 Irving St. N.W., Washington, District of Columbia*, 20422, United States of America

A total of 35 patients have been entered to date. All required cultures were obtained in 31 of the 35 patients. All blood cultures were sterile after 7 day incubation in 28 of the 31 patients. The types of microorganisms in clinical courses of the 3 patients with positive cultures indicated that these were probably cases of contamination. There have been no complications. The study will continue unmodified. Per suggestion of the Human Studies Subcommittee, a separate informed consent is not used.

4. CMV INFECTION IN THE ALLOGENIC MARROW GRAFT RECIPIENTS

Thomas, E. D., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This is part of a broader project. A summary of this subproject is not available.

5. CMV INFECTION IN BMT RECIPIENTS

Lopez, C., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

6. ENVIRONMENTAL STUDIES TO PREVENT HOSPITAL ACQUISITION OF POTENTIALLY DANGEROUS MICROFLORA

Young, V. M., Friedman, N. R., Schimpff, S. C., Moody, M. R., Newman, K., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Research Microbiology Section, *Baltimore, Maryland*, 21201, United States of America

The purpose of this continuing study is to monitor the hospital environment and protective isolation rooms for sources of microorganisms which can, given the opportunity, colonize and eventually infect the host-impaired cancer patient. As such sources are detected, procedures are instituted to prevent recurrence. Examples of problem areas detected last year are: 1) Certain contaminated foods, 2) contaminated ice from hospital kitchen, 3) contaminated Coca cola, 4) improperly cleaned ICU rooms and 5) contaminated denture cups.

7. RESEARCH ACTIVITIES DIRECTED TOWARD IMPROVEMENT OF MICROBIOLOGY LABORATORY TECHNIQUES

Young, V. M., Moody, M. R., Hargadon, M. T., Thomas, G. M., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Research Microbiology Section, *Baltimore, Maryland*, 21201, United States of America

The project provides for development of methodology and its implementation in response to the needs of patient care and/or the microbiology laboratory. Two tests for the detection of Clostridium difficile in patients with diarrhea have been evaluated and set up. API systems have been tested and are being used for yeast and anaerobe identifications. The API system for identification of Enterobacteriaceae was compared to the MIC 2000

identification system with similar results. An immunodiffusion kit for detection of antibodies against Aspergillus is under evaluation and FA techniques for identification of Legionella pneumophilia, Listeria, and Candida albicans have been readied for use.

8. STUDIES ON CANCER PATIENT MICROBIAL FLORA - ACQUISITION, COLONIZATION AND INFECTION

Young, V. M., Moody, M. R., Schimpff, S. C., Wade, J. C., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Research Microbiology Section, *Baltimore, Maryland,* 21201, United States of America

The purpose of this project is to monitor the patients' microbial flora which may give rise to infection, to determine sources of hospital acquired flora when possible, and to study characteristics of unusual organisms of clinical significance. Such organisms may be subspeciated by phage typing, serotyping or biotyping to allow determination of spread. A review of cultures, particularly blood cultures, revealed that during the past year gram-positive cocci outnumbered gram-negative bacilli as a cause of bacteremias. Staphylococcus epidermidis and streptococci both increased significantly in numbers. Antibiotic resistant coryneform bacteria are still encountered in the patients and further studies have been carried out to evaluate their characteristics. Nasal surveys for filamentous fungi confirmed the presence of the organisms in the air as has been shown in air samples (Project No. Z01 CM 06938-11 COB). Staphylococcus aureus surveys of personnel showed the carrier rate to be sharply decreased.

BIBLIOGRAPHIC REFERENCES: Schimpff, S.C. and Young, V.M. Epidemiology and prevention of infection in the compromised host, Clinical approach to infection in the immunocompromised host, R.H. Rubin and L.S. Young, Plenum Publishing Corp. N.Y. in press, 1980. Young, V.M., Moody, M.R. and Morris, M.J. Phase variation in the genus Serratia. J. Med. Microbiol. in press, 1980.

B. DIAGNOSIS OF INFECTIOUS DISEASE

9. BACTERIAL TRANSLOCATION FROM THE GI TRACT AS A PRIMARY MECHANISM OF INFECTION IN THE IMMUNOSUPPRESSED CANCER PATIENT

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Infection has long been recognized as a major cause of morbidity and mortality in patients with malignant disease, especially leukemia. It is hypothesized that a large portion of infectious disease of cancer patients is caused by bacteria translocating from the patients' own gastrointestinal (GI) tracts. Bacterial translocation is defined as the passage of viable bacteria from the GI tract through the GI mucosa to other organs, such as the mesenteric lymph nodes (MLN), spleens, livers, etc. The PI has demonstrated that certain indigenous bacteria remain confined to the GI tracts of healthy, specific pathogen-free (SPF) mice due to: (a) The host's immune system, and (b) the control of GI population levels of certain bacteria by other antagonistic members of the normal flora. When these defense mechanisms are disrupted, certain indigenous bacteria translocate from the GI tract to other organs. The proposed research will characterize further the role of the thymus and T-cell mediated immunity in inhibiting bacterial translocation from the GI tract. It will be determined if adoptively transferred T-cells can inhibit bacterial translocation in SPF or gnotobiotic athymic (nude) mice, and whether thymectomy of SPF mice will promote bacterial translocation. It will be determined whether the promotion of bacterial translocation in mice receiving immunosuppressive chemotherapeutic agents such as cyclophosphamide, methotrexate, 5-fluorouracil, etc. is due to immunosuppression or to some other pharmacological activity. The proposed research will demonstrate whether the increase in bacterial translocation after the administration of certain antibiotics, such as penicillin, metronidazole, clindamycin etc., is caused by overpopulation of the translocating bacteria in the GI tract. Also, it will be determined if these antibiotics and immunosuppressive agents can act synergistically to promote bacterial translocation and infectious disease. Finally, attempts will be made to eliminate viable translocating bacteria from the mesenteric lymph nodes and other organs with absorbable antibiotics. This research will provide information concerning how disruptions in the host's immune response and in the ecology of the indigenous flora of the GI tract can cause infectious disease in cancer patients caused by bacteria normally present in the patients' own GI tracts.

10. CMV INFECTION AS A CAUSE OF FEVER IN PATIENTS WITH LEUKEMIA

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The purpose of this study is to determine the role of CMV infection in leukemic patients with unexplained fever. Potential benefits include clarification of the etiology of an unexplained febrile illness, determination of the role of CMV infection in the leukemic population, definition of a population in which antiviral therapy might be indicated, and determination of any risk factor for CMV infection in this population.

Patients with newly diagnosed leukemia and lymphoma will be entered into the study after informed consent. Serum antibody titers, lymphocyte transformation and blood, throat, and urine cultures for CMV will be performed periodically and with each febrile illness.

The techniques required for this project have been practiced and refined for the past four months.

11. BRONCHIAL BRUSHING FOR PULMONARY INFILTRATES IN PATIENTS WITH CANCER

Aisner, J., Schimpff, S. C., Young, V. M., Wiernik, P. H., Wade, J. C., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Section of Infection Research, *Baltimore, Maryland,* 21201, United States of America

The myelosuppressed patient with cancer may develop pneumonias which are difficult to diagnose. Thus, aggressive diagnostic procedures are warranted. This study utilized a stepwise, orderly method for diagnosing unexplained pulmonary infiltrates utilizing transtracheal aspiration, transtracheal bronchial brushing, fiberoptic bronchoscopy or percutaneous lung biopsies when other methods have failed. Transtracheal aspiration led to diagnosis in about 20-30% of cases. Bronchial brushing yielded diagnostic information in about 30% of cases overall and in nearly 80% of those ultimately proven to have infectious problems. Thirty to 40% of cases are ultimately shown to have noninfectious etiologies such as metastases, interstitial fibrosis or subsegmental collapse. Among the infectious etiologies the diagnosis included a variety of micro-organisms: bacterial, protozoal and fungal. Significant but non-fatal complications occurred and were acceptable risks for the patient population. There was no mortality associated with the procedures, and despite pancytopenia, bleeding was a problem in only 3 patients. This step-wise aggressive diagnostic procedure has proven to be clinically efficacious in 80% of the patients with ultimately documented pneumonias and is now considered standard therapy.

12. CANDIDA ALBICANS ANTIGENS AND ANTIBODIES

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Nosocomial infections account for billions of dollars in hospital costs per year. Candidiasis is a problem of considerable importance in patients undergoing many forms of cancer therapy, including immunosuppression, chemotherapy and heroic surgery. The diagnosis of disseminated candidiasis remains an enigma for the clinician. In the past 2 1/2 years we have greatly improved the serodiagnosis of this disease. At present we are identifying the antigens from the mycelial phase of this antigenically complex microorganism which appear to be important proteins to which only patients with disseminated disease produce antibodies.

The aims of this proposal are: 1) To isolate and characterize these antigens; 2) to establish their biological function; 3) to use antibodies produced to these antigens for antigen detection.

BIBLIOGRAPHIC REFERENCES: Syverson, R.E., Buckley, H. R. Increasing the predictive value of the precipitin

test for deep-seated candidiasis. Accepted for publication, Am. J. Clin. Path., 1978.

13. INFECTION RESEARCH IN ONCOLOGY

Schimpff, S. C., Aisner, J., Wiernik, P. H., Young, V. M., Schiffer, C. A., Newman, K., Wade, J. C., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Section of Infection Research, *Baltimore, Maryland*, 21201, United States of America

Infection is the leading cause of morbidity and mortality in patients with acute leukemia and a major cause in other types of advanced malignancies. The aim of this program is an integration of research, education, and patient care with regard to the infections arising in patients with cancer. The research areas include infection epidemiology, diagnosis, prevention and treatment. Education includes teaching BCRC clinical associates the fundamental problems and techniques for infection management, teaching the nursing staff basic prevention and treatment modalities, and teaching the University of Maryland Infectious Disease fellows and students concepts of infection control in the tumor patient. Patient care includes patient education in infection prevention in addition to infection diagnosis, prevention and management.

BIBLIOGRAPHIC REFERENCES: Schimpff, S.C.: Infection prevention during granulocytopenia. In Remington, J.S. and Swartz, M.N. (Eds.): Current Clinical Topics in Infectious Diseases. New York, McGraw-Hill Book Company, 1980, pp. 85-106. Schimpff, S.C. and Wiernik, P.H.: Infection in cancer patients (predisposing factors, sites, organisms and general approaches to diagnosis). In Silver, R.T. (Ed.): Topics in Cancer. New York, Physician Programs, Inc., 1980 (in press).

14. EVALUATION OF THE TYPES AND CAUSES OF INFECTIOUS DISEASES IN CANCER PATIENTS

Schimpff, S. C., Wade, J. C., Newman, K. A., Wiernik, P. H., Young, V. M., Overholser, D., Peterson, D., Applefeld, M., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Section of Infection Research, *Baltimore, Maryland*, 21201, United States of America

Infection is the leading cause of morbidity and mortality in patients with acute leukemia and a major cause in other types of advanced malignancies such as Hodgkin's disease and oat cell carcinoma of the lung. The aims of this project are to catalogue and identify the infections, identify the predisposing factors and evaluate new techniques for more rapid and/or accurate diagnosis of infection. This program has been in progress for over eight years and has allowed meaningful evaluation of the types of infection occurring in different types of tumor patients. Specific problems have been identified such as the nature of hospital acquisition of potential pathogens including bacteria and fungi. This epidemiologic data has allowed appropriate and logical development of infection prevention techniques and application of newer methods of infection diagnosis such that there has been a reduction of infection morbidity and mortality.

BIBLIOGRAPHIC REFERENCES: Schimpff, S.C.: Infection in patients with cancer. In Lichtman, M.A. and Wiernik, P.H. (Eds.): The Science and Practice of Clinical Medicine, New York, Grune and Stratton, 1980 (in press). Wade, J.C. and Schimpff, S.C.: Infections in patients with suppressed cellular immunity. In Klastersky, J. and Staquet, M. (Eds.): Supportive Care in Cancer Patients. I. New York, Raven Press, 1980 (in press).

C. ANTIBIOTIC THERAPY OF INFECTIONS

15. THE PREVENTION OF INFECTION IN GRANULOCYTOPENIC PATIENTS

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OBJECTIVE: To improve the management of patients during episodes of neutropenia by: a. Preventing infection, b. early diagnosis and therapy of infections, particularly fungal infections.

APPROACH: All adult granulocytopenic patients at the Health Sciences Centre, Winnipeg are entered into the study. At present there are between 70 and 90 patient episodes anually. All patients receive oral prophylaxis with trimethoprim/sulfamethoxazole and are randomized to regimens to prevent fungal colonization. Also, patients are randomized to receive lithium in order to determine its efficacy in modifying granulocytopenia.

On becoming febrile, the patient is randomized to one of two wider-spectrum antibacterial regimens. If the patient fails to respond to therapy, randomization to granulocyte transfusions occurs. Prospective studies to detect antigens to both Candida and Aspergillus are also under way. In addition, the efficacy of miconazole and amphotericin B in Aspergillus infection is still uncertain and needs further investigation.

PROGRESS: During the past 18 months, we have published our studies on trimethoprim/sulfamethoxazole prophylaxis in granulocytopenic patients. We have completed a study randomizing patients to either trimethoprim alone or the combination of trimethoprim/sulfamethoxazole with prospective clinical data that shows trimethoprim alone to be an effective prophylaxtic agent. However, bacteriologic data suggests that trimethoprim alone permits the emergence of resistant organisms. We have reviewed 66 deaths occurring during granulocytopenic episodes in 270 patients. One-half of these patients received trimethoprim/sulfamethoxazole prophylactically prior to death and none of these patients died with gram-negative sepsis. In addition, we have shown that nystatin has minimal effect in preventing colonization with Candida species.

We have developed an animal model of granulocytopenia that mimics human disease. Rats die during the second week of granulocytopenia with bacteremic sepsis. Both trimethoprim/sulfamethoxazole and trimethoprim alone prevent deaths, and contribute to enhanced survival of the animals. We intend to use this model to study further mechanisms by which antibacterial prophylaxis delays sepsis and death during granulocytopenia.

16. INFECTIOUS COMPLICATIONS OF MALIGNANCY - PREVENTION, DIAGNOSIS AND THERAPY

Pizzo, P. A., Robichaud, K., Straus, S., Glaubiger, D., Nelson, D., Kraemer, K., Kramer, B., Gill, F. A., Jones, A. E., Segal, E., Hoffman, F. A., Spiegel, R., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Infectious Disease Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

Infection is the major cause of morbidity and mortality in patients with malignant disease. We are developing and evaluating the utility of various techniques and procedures to reduce the incidence of severe infection in cancer patients. The role of oral absorbable antibiotic prophylaxis is being evaluated in patients receiving standard doses of chemotherapy, and the role of protected environments (laminar air-flow room isolators) is being studied in patients receiving intensive chemotherapy. We are also evaluating new methods for detecting occult infections in neutropenic patients, e.g., gallium scanning in conjunction with white cell transfusion and the ELISA inhibition assay for fungal antigen. Empiric and specific antibiotic treatment of granulocytopenic patients with fever of unknown origin or proven infections is being prospectively studied, and the role of newer antimicrobial agents is also being investigated. The role of chemically defined immunoregulatory agents is being evaluated in in vitro and in vivo models to develop methods of improving host defenses following immunosuppressive chemotherapy and reduce the incidence and severity of infectious complications.

BIBLIOGRAPHIC REFERENCES: Klastersky, J., Schimpff, S.C., Glauser, M.P., Young, L.S., Zinner, S., Gays, H., Pizzo, P.A., Bodey, G.P.: Prevention and therapy of infection in cancer patients. In Nelson, J.D. and Grassi, C.: Current Chemotherapy in Infectious Disease. Washington, D.C., Am. Soc. Microbiology, 180, pp. 1427-1434. Pizzo, P.A., Ladisch, S., Robichaud, K.: Treatment of gram-positive septicemia in cancer patients. Cancer 45: 206-207, 1980.

17. ANTIBIOTIC THERAPY FOR FEVER OF NEUTROPENIC CANCER PATIENTS

Bjornsson, S., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York*, 14263, United States of America

This is part of a broader project. A summary of this subproject is not available.

18. FEVER AND ANTIMICROBIAL THERAPY IN GRANULOCYTOPENIC PATIENTS

Kramer, B. S., Rand, K., Weiner, R., Ross, W., Noyes, W., Kitchens, C., Johnson, A. G., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *Gainesville, Florida*, 32601, United States of America

In the past 12 months we have accrued 45 patients to the prophylactic phase and 73 patients to the therapeutic phase of the fever study. Of these, 21 patients at the GVAH have entered the prophylactic phase and 28 patients at the GVAH have entered the therapeutic phase. In VA patients no unexpected adverse reactions to the study drugs have been observed. There were two episodes of rash linked to the prophylactic antibiotics and none secondary to the therapeutic antibiotics. Amphotericin has uniformly caused chills and fever when used. All of these adverse reactions were anticipated as possible drug toxicities. There were no treatment-related deaths.

It is too early to analyze the data for statistical differences between randomized groups. We anticipate that accrual will be complete within the next 24 months. A positive aspect of the study has been the faster reaction time of housestaff in placing febrile granulocytopenic patients on broad spectrum antibiotics.

19. EPIDEMIOLOGY AND ANTIMICROBIAL PROPHYLAXIS OF INFECTION

Young, L. S., University of California, Los Angeles Campus, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California*, 90024, United States of America

This is part of a broader project. A summary of this subproject is not available.

20. THERAPY OF SUSPECTED BACTERIAL INFECTION IN GRANULOCYTOPENIC PATIENTS WITH CANCER

Schimpff, S. C., Wade, J. C., Young, V. M., Fortner, C. L., Moody, M. R., Wiernik, P. H., Newman, K. A., Standiford, H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Section of Infection Research, *Baltimore, Maryland*, 21201, United States of America

A series of consecutive antibiotic trials for suspected sepsis in granulocytopenic cancer patients began in 1969 and continues to the present. Initial evaluations proved the usefulness of carbenicillin and gentamicin and later trials, including a large multi-institutional trial, indicated that carbenicillin (ticarcillin) plus gentamicin had the best efficacy-to-toxicity ratio of the three possible two-drug combinations of carbenicillin (ticarcillin), gentamicin and cephalothin. The following two-drug combinations were therefore evaluated: ticarcillin plus gentamicin, ticarcillin plus amikacin and ticarcillin plus netilmicin. In 183 consecutive patient-trials, the efficacy was high and the toxicity minimal. With the addition of early granulocyte transfusions for poor risk patients, a response rate of over 90% was achieved. A new penicillin derivative, mezlocillin, with exceedingly broad activity was utilized alone in 50 consecutive patients but proved less than satisfactory in the absence of concomitant aminoglycoside therapy. Therefore, ticarcillin plus amikacin became standard therapy to which piperacillin (a new broad spectrum penicillin) plus amikacin and moxalactam (a new broad spectrum cephalosporin) plus amikacin have been compared with excellent results.

BIBLIOGRAPHIC REFERENCES: Wade, J.C. and Schimpff, S.C.: Antibiotic therapy for febrile granulocytopenic patients. In Klastersky, J. and Staquet, M. (Eds.): Supportive Care in Cancer Patients. I, New York, Raven Press, 1980 (in press). Love, L.J., Schimpff, S.C., Schiffer, C.A. and Wiernik, P.H.: Improved prognosis for granulocytopenic patients with gram-negative bacteremia. Am. J. Med. 68:643-648, 1980.

21. ANTIBIOTIC PROPHYLAXIS IN THE MANAGEMENT OF ACUTE LEUKEMIA AND ITS EFFECTS ON THE PATIENTS' MICROFLORA

Catovsky, D., Darrell, J., Medical Research Council, Leukaemia Unit, Dept. of Bacteriology, *Du Cane Rd., c/o Royal Postgrad. Med. Sch., London W12 0HS, England, United Kingdom*

A combined clinicobacteriological study is proposed to examine whether the prophylactic use of co-trimoxazole alone or in combination with non-absorbable antibotics is effective in decreasing the rate of infection in neutropenic patients treated for acute leukemia. The laboratory studies will be directed at investigating changes in gut and other body microflora resulting from the above regimens and seeking correlations between bacteriology data and clinical outcome.

It is proposed to enter in the study all patients suffering from acute myeloid leukemia admitted for cytotoxic treatment in the Dacie ward during a 2-year period. All patients will, on admission, be put on an antifungal regimen and on a rigorous regimen for skin, nose and throat antisepsis. They will be randomized to receive 24 hours later either: (a) co-trimoxazole alone twice daily, or (b) co-trimoxazole as above plus gut decontamination with framycetin and colistin, four times a day. Patients will be monitored with mutliple swabs and samples from various tissues. Bacteriological screening will be done twice weekly. Fecal specimens will be cultured aerobically and anaerobically and gas liquid chromatography (GLC) will be performed on these. End-point: (1) Clinical remission with recovery of neutrophils to 1 x 10 to the 9th power over 1 or (2) sustained fever (greater than or equal to 38 degrees C) for 2 hours and the commencement of systemic antibiotics will constitute the end points for clinical analysis.

22. AN EVALUATION OF THE EFFECT OF CHEMOTHERAPY AND ORAL ANTIBIOTICS ON GASTROINTESTINAL FUNCTION

Grove, W. R., Fortner, C. L., Schimpff, S. C., Newman, K. A., Lamy, P. P., Wiernik, P. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Research Pharmacy Section, *Baltimore, Maryland*, 21201, United States of America

The objective of this study is to evaluate the effect of chemotherapy and oral antibiotics on gastrointestinal function in a population of patients with acute nonlymphocytic leukemia in remission.

Eligible patients are those who are receiving the chemotherapy combination of thioguanine and cytosine arabinoside as maintenance chemotherapy and any of the following combinations of oral antibiotics for infection prevention: gentamicin plus nystatin; gentamicin plus vancomycin plus nystatin; nalidixic acid plus nystatin; trimethoprim sulfamethoxazole plus nystatin.

The following laboratory tests are performed as a baseline, repeated at the end of the chemotherapy course and again when patients are given oral antibiotics: serum carotene, serum vitamin A, serum folic acid, serum D-xylose (2 hrs) and urine D-xylose (5 hrs).

Sixteen patients have been entered on study. Seven patients have completed the sequence of laboratory tests. Eight patients failed to complete the tests, mostly due to the need for hospitalization to receive systemic empiric antibiotics. One patient remains on study. Additional patients will be entered on the study as they begin their maintenance courses of chemotherapy. It is too early to evaluate the data.

23. NEW ANTIBIOTICS FOR INFECTION IN CANCER PATIENTS

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This is part of a broader project. A summary of this subproject is not available.

24. ANTIBIOTIC STUDIES - EVALUATION OF NEW DRUGS AND THEIR CHARACTERISTICS

Moody, M. R., Young, V. M., Schimpff, S. C., Tillman, G. L., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Research Microbiology Section, *Baltimore, Maryland*, 21201, United States of America

'Normal' microflora can cause serious infections in cancer patients and control of infections by prevention or elimination is essential. This study objective is to evaluate the in vitro effectiveness of new antibiotics against these bacteria and to monitor the susceptibility trends to antibiotics already in use. MK0787, an analogue of thienamycin, was a highly potent inhibitor of enterobactera, P. aeruginosa and gram-positive cocci, including those strains resistant to six lactam antibiotics; i.e., piperacillin, ticarcillin, carbenicillin, mezlocillin, azlocillin, and BAY K4999. Incidence of mezlocillin-resistant strains decreased to pre-use levels 1 year after mezlocillin use discontinuation. Piperacillin

patterns remained the same. Carbenicillin resistance has increased among strains of P. aeruginosa and E. coli, as well as ticarcillin resistance among the latter strains and Klebsiella spp. The Moxalactam-amikacin combination exerted a synergistic or partially synergistic effect on about half of enterobacterial strains tested and about 90% of P. aeruginosa strains. Amikacin-piperacillin was also synergistic or partially so for most of the enterobacteria as well as P. aeruginosa. Moxalactam-piperacillin was usually synergistic for P. aeruginosa but not necessarily so for the enterobacteria.

BIBLIOGRAPHIC REFERENCES: Moody, M.R., Young, V.M., Schimpff, S.C., Purvis, D.S. and Wiernik, P.H. In vitro antibacterial activity of four aminoglycosides and two semisynthetic penicillins on fresh clinical isolates from cancer patients. European Journal of Cancer, 15: 23-33, 1979. Moody, M.R., Young, V.M., Morris, M.J., and Schimpff, S.C. In vitro activity of miconazole, miconazole nitrate, and ketaconazole alone and combined with rifampin against Candida spp. and Torolopsis glabrata recovered from cancer patients. Antimicrobial agents and Chemotherapy. In press, 1980.

D. PROTECTIVE ENVIRONMENTS AND OTHER PROPHYLAXIS OF INFECTION IN CANCER PATIENTS

25. LAMINAR AIR FLOW PROTOCOLS

Thomas, E. D., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington,* 98104, United States of America

This is part of a broader project. A summary of this subproject is not available.

26. LAMINAR AIR FLOW STUDIES

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This is part of a broader project. A summary of this subproject is not available.

27. QUANTITATIVE EVALUATION OF PROTECTED ENVIRONMENT

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OBJECTIVE: Determine whether protected environments plus prophylactic antibodies (PEPA) during chemotherapy for sarcomas, breast carcinoma, and malignant lymphoma reduce the risk of infection and permit the administration of higher doses of chemotherapy, and whether higher doses of chemotherapy result in higher response rates, longer duration of response, and longer survival.

28. CANCER CLINICAL RESEARCH

Hickey, R. C., Bodey, G. P., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas,* 77030, United States of America

This Clinical Research Center Grant has been prepared to serve as a major source of support for the Clinical Research Center which consists of a 22 bed research unit and a 20 bed laminar flow unit. Major divisions of clinical research which will be emphasized include the diagnosis, biology, clinical presentation and the therapy of human cancer. Included are protocols to evaluate cellular kinetics of tumor cells, diagnosis and management of hormone-producing tumors, evaluation of new drugs and drug regimens in malignant diseases, the use of laminar air flow rooms and prophylactic antibiotics in the chemotherapy of leukemia and breast cancer, development of new techniques for study of the immunology of cancer and its immunotherapy, and exploration of the pharmacology of antitumor drugs. Through intradisciplinary research in a specialized setting, it is anticipated that further progress will be made in the management of the cancer patient.

29. PROTECTED ENVIRONMENT IN MYELOSUPPRESSING CHEMOTHERAPY (HUMAN)

Rosenthal, C. J., State University of New York, Downstate Medical Center, School of Medicine, Dept. of Medicine, *450 Clarkson Ave., Brooklyn, New York,* 11203, United States of America

This is part of a broader project. A summary of this subproject is not available.

30. SEPARATION OF BLOOD BY CONTINUOUS CENTRIFUGE

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This project is concerned with the continuous flow manipulation of cellular and humoral blood components.

Methods of improving granulocyte collection from normal donors using shunts and centrifugation will be investigated.

A prospectively randomized controlled study will evaluate prophylactic granulocytes for patients over 50 years of age receiving initial remission induction for acute leukemia.

A prospectively randomized study will compare the effect of the decision to protect patients undergoing allogeneic marrow transplantation with laminar air flow isolation or prophylactic granulocyte transfusions.

The effects of plasma exchange and continuous flow plasma immunoperfusion on immune disease and malignancy will be studied in dogs and man.

31. PROTECTIVE ENVIRONMENT AND GRANULOCYTE TRANSFUSION (HUMAN)

Buckner, C. D., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington,* 98104, United States of America

This is part of a broader project. A summary of this subproject is not available.

32. INFECTIOUS COMPLICATIONS OF MALIGNANCY - PREVENTION, DIAGNOSIS AND THERAPY

Pizzo, P. A., Robichaud, K., Straus, S., Glaubiger, D., Nelson, D., Kraemer, K., Kramer, B., Gill, F. A., Jones, A. E., Segal, E., Hoffman, F. A., Spiegel, R., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Infectious Disease Section, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

The summary for this project is under entry no. 16.

33. GERM-FREE TECHNIQUES APPLIED TO ADOPTIVE IMMUNOTHERAPY

Truitt, R. L., Bortin, M. M., Mount Sinai Medical Center, Winter Research Laboratory, *950 N. 12th St., Milwaukee, Wisconsin,* 53201, United States of America

The overall objective of this research is to develop an effective treatment plan using adoptive immunotherapy in combination with chemoradiotherapy for spontaneous leukemia in AKR mice. In particular, the beneficial effects of bacterial decontamination and isolation in a protected environment are being studied.

Procedures for elimination of bacteria from the intestinal tract have been successfully applied to AKR mice after diagnosis of spontaneous acute T cell leukemia. Leukemic mice are rendered bacteria-free by continuous treatment per os with high dose antibiotics; a sterile laminar airflow environment is used to protect decontaminated mice from exogenous microorganisms. Leukemia remission induction with chemotherapy is essential to keep a significant proportion of leukemic mice alive during decontamination. For hematopoietic support and adoptive immunotherapy, mice undergoing decontamination are injected with bone marrow cells from conventional H-2 compatible or incompatible donor mice. Adoptive immunotherapy when applied to decontaminated leukemic AKR mice in remission can result in significant long-term leukemia-free survival without apparent secondary disease. Leukemia-free chimeras can be returned to the conventional environment. Experiments using the experimental treatment model to answer important questions concerning the clinical applicability of this model are continuing.

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edith, eds., CRC Press, West Palm Beach, Fla., 1979, in press. Truitt, R.L., Bortin, M.M. and Rimm, A.A.: Successful Adoptive Immunotherapy of AKR Spontaneous T Cell Leukemia following Antibiotic Decontamination and Protective Isolation. Zentralblatt fur Bakteriologie, in press, 1979.

34. STUDY AND TREATMENT OF CANCER IN THE YOUNG

Levine, A. S., Poplack, D. G., Glaubiger, D., Pizzo, P. A., Deisseroth, A. B., Magrath, I. T., Simon, R., Ziegler, J. L., Rosenberg, S. A., Glatstein, E., Chabner, B., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Pediatric Oncology Branch, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

Acute leukemia, non-Hodgkin's lymphomas (e.g., Burkitt's), neuroblastoma, rhabdomyosarcoma, osteosarcoma, Ewing's sarcoma and aplastic anemia are studied. In the treatment of leukemia, we have devised therapeutic regimens which may allow maximum tumor cell kill while minimizing sequellae. Emphasis is on tailoring treatment to individual prognostic variables, and improving the therapeutic ratio in CNS prophylaxis. In treating the solid tumors, we have developed combined modality approaches to primary disease. In refractory tumors, we are studying the utility of high-dose-therapy and the role of supportive care (platelet and white cell transfusion, laminar-flow protection, autologous bone marrow rescue, total parenteral nutrition) in permitting such therapy. Phase I-II trials are also conducted in refractory tumors; agents include ICRF-187, poly I:C/poly-l-lysine, dihydroxyanthracenedione, and 2'-deoxycoformycin. We are exploring the biology of selected tumors, including kinetics, immunology, virology, tumor markers, genetics, biochemistry, and pharmacology. Also studied are the effects of cancer and its treatment on growth, development, and organ function. The psychosocial concomitants of cancer are explored.

BIBLIOGRAPHIC REFERENCES: Glaubiger, D., Makuch, R., Schwarz, J., Levine, A.S., and Johnson, R.E.: Determination of prognostic factors and their influence on therapeutic results in patients with Ewing's sarcoma. Cancer 45: 2213-2219, 1980. Shackney, S.E., Bunn, P.A., Ford, S.S., Erickson, B., Ross, W.E., and Levine, A.S.: A study of drug-induced kinetic perturbations in the marrow of a patient with neuroblastoma. Cancer 45: 882-892, 1980.

35. THERAPY OF FUNGAL INFECTIONS IN PATIENTS WITH CANCER

Aisner, J., Schimpff, S. C., Wade, J. C., Wiernik, P. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Section of Infection Research, *Baltimore, Maryland*, 21201, United States of America

Fungal infection in cancer patients are difficult to diagnose and such diagnoses are frequently only made at necropsy. Earlier, aggressive diagnostic procedures (see no. 06913 regarding bronchial brushing) have improved diagnostic accuracy and earlier therapy has become possible. Evaluation of epidemiologic factors has also identified the at risk population: Patients with positive nose cultures may have invasive disease and patients with sterile nose cultures are at risk of developing it. With the establishment of earlier diagnostic tests for systemic mycoses, we are testing the addition of rifampin to amphotericin-B to evaluate the known in vitro synergistic effect against many fungi. This treatment is used for suspected and documented fungal infections. Fifty patients have been randomly allocated to date, but after stratification for the various fungal infections, there are too few patients from which to draw meaningful conclusions other than that early application of therapy continues to be the best approach to infection resolution.

II. IMMUNOLOGICAL ASPECTS OF SUPPORTIVE CARE OF CANCER PATIENTS

A. BONE MARROW TRANSPLANTATION

1. HUMAN BONE MARROW TRANSPLANTATION

36. BONE MARROW TRANSPLANTATION IN THE TREATMENT OF ACUTE MYELOID LEUKEMIA

Gordon Smith, E. C., Harris, R. A., University of London, Royal Postgraduate Medical School, Dept. of Haematology, *c/o Hammersmith Hospital, Du Cane Rd., London W12 0HS, England, United Kingdom*

OBJECTIVE: To assess the value of allogeneic bone marrow transplantation in the treatment of acute myeloid leukemia.

APPROACH: The initial part of the program is to study the complications of bone marrow transplantation so that some of the more serious side effects may be anticipated and prevented. At this stage virological studies together with recurrent lung and intestinal function studies are being carried out.

PROGRESS: The numbers of patients investigated since June 1978 are as yet too small to draw conclusions. Methods for measuring lung function and intestinal absorption in sterile conditions have been developed.

37. REMOVAL OF RESIDUAL LEUKEMIC CELLS FROM REMISSION BONE MARROW PRIOR TO AUTOLOGOUS TRANSPLANTATION

Hoffbrand, A. V., Janossy, G., Prentice, H. G., University of London, Royal Free Hospital of Medicine, Dept. of Haematology, *8 Hunter St., London N.W.3, England, United Kingdom*

OBJECTIVE: To determine whether it is feasible to treat selected patients with leukemia by autologous bone marrow transplantation after removal of leukemic cells in vitro.

APPROACH: Purified antibodies to antigens on leukemic or lymphoma cells, e.g., thymocyte antigens or light chain of immunoglobulins, will be prepared and used to remove malignant cells in vitro from bone marrow of patients with these diseases. After total body irradiation or cytotoxic therapy, the marrow will be used to rescue the patients.

PROGRESS: Initial studies of bone marrow freezing and preparation of purified antisera are under way.

38. EVALUATION OF BONE MARROW TRANSPLANT PATIENTS FOR ACUTE LEUKEMIA

Barrett, A. J., Kay, H. E., Powles, R., Royal Marsden Hospital, Leukaemia Unit, *Downs Rd., Sutton SM2 5PT Surrey, United Kingdom*

OBJECTIVE: When patients with acute leukemia in relapse are transplanted with bone marrow many die within the first few weeks after transplantation from a variety of complications related to their poor clinical state. It was therefore decided to evaluate the therapeutic role of bone marrow transplantation in treating patients with acute myeloid leukemia in remission and acute lymphoblastic leukemia in the second remission.

APPROACH: A schedule for pre- and post-bone marrow transplantation management and laboratory studies was set up. Patients received cyclophosphamide 60 mg per kilogram on two successive days and total body irradiation to 1000 rad at a dose rate of 2.5 rad per minute, followed by bone marrow transplantations from an HLA identical mixed leucocyte culture compatible sibling. After transplantation patients received either methotrexate or Cyclosporin-A as prophylaxis against graft-versus-host disease. Follow-up included regular bone marrow examinations for evidence of leukemia, bone marrow colony-forming assays and liver function tests, and skin or rectal biopsies when graft-versus-host disease was suspected.

PROGRESS: Between September 1977 and October 1978 14 patients with acute non-lymphoblastic leukemia and four patients with acute lymphoblastic leukemia were transplanted. Four patients (2 ALL, 2 AML) were transplanted in relapse. Two patients died from early complications of transplantation and two died nine and eleven months after transplantation from relapse of the original leukemia. Of the 12 patients with AML

grafted in remission, three have died from graft-versus-host disease, two have relapsed (one of them is dead). Two patients with ALL were grafted in remission, one patient died from obscure causes possibly related to graft-versus-host disease, the other survives with graft-versus-host disease. While it is too early to evaluate the overall success of this procedure it seems clear that transplantation in remission is associated with a much higher early survival. This is related to the lack of major clinical problems in remission patients undergoing marrow transplantation.

39. USE OF BONE MARROW TRANSPLANTS IN THE TREATMENT OF ACUTE LEUKEMIA

Kay, H. E., Powles, R. P., Barrett, A. J., Royal Marsden Hospital, Leukaemia Unit, *Downs Rd., Sutton SM2 5PT Surrey, United Kingdom*

OBJECTIVE: To explore the value of bone marrow transplantation in the treatment of acute leukemia, especially acute myeloid leukemia in first remission.

APPROACH: The protocol is that used in Seattle, i.e., high dose cyclophosphamide and whole-body irradiation but with two main differences: a) the dose-rate of irradiation will be slow (2.5 rad/min) and unfractionated; b) alternative means to prevent GvH reactions are being explored.

PROGRESS: The program is continuing although Dr. Barrett, the L.R.F. fellow, has left. Early results indicate that BM transplants are well-tolerated by patients in first remission. Of 11 with AML in first remission there has been one relapse (an identical twin), two fatal GvH reactions, and eight continue in remission at periods of four weeks to 18 months; mild or chronic GvH is present in two.

40. AN EVALUATION OF THE ROLE OF ALLOGENEIC AND AUTOLOGOUS MARROW TRANSPLANTATION IN THE MANAGEMENT OF MALIGNANT DISEASES

Biggs, J. C., Ma, D., Pun, A., Johnson, L., Bashir, H., Penny, R., Vincent, P., St. Vincent's Hospital, Dept. of Haematology, *Victoria St., Darlinghurst, N.S.W. 2010, Australia*

OBJECTIVE: In this project, the role of allogeneic transplantation in the management of leukemia and lymphoma will be evaluated; furthermore, the role of autologous marrow transplantation will be evaluated in the management of acute leukemia, chronic granulocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma and certain solid tumors e.g., sarcomas, ovarian carcinoma and testicular tumors.

APPROACH: (a) An evaluation of cryopreservation methods is being undertaken. (b) Techniques for the measurement of viability following thawing of marrow cells are being established. (c) Allogeneic transplants following total body irradiation are being studied in acute adult leukemia during the first relapse. (d) Patients' remission marrow in acute leukemia and marrow in chronic granulocytic leukemia are being stored and used after thawing for autologous transplantation during subsequent therapy of acute relapses. (e) Cryopreservation of marrow in patients with sensitive solid tumors is being undertaken for subsequent autologous transplantation during chemoradiotherapy for relapse.

41. AUTOLOGOUS BONE MARROW TRANSPLANTATION AS AN ADJUNCT TO ABLATIVE CHEMOTHERAPY FOR THE TREATMENT OF ACUTE LEUKEMIA

Gorin, N. C., Duhamel, G., Najmam, A., Salmon, C., Muller, J. Y., Petit, J. C., Hopital Saint-Antoine, Dept. of Hematology, *184, rue du Faubourg Saint-Antoine, 75012 Paris, France*

Autologous bone marrow transplantation is now feasible in man and allows higher dosage of chemotherapy and/or radiotherapy for the treatment of malignant tumors, without the risk of lethal toxicity from myelosuppression.

The objectives of the present study are to harvest and store autologous marrow from patients with acute leukemia (AML, ALL, acute monoblastic leukemia, CML) as soon as the first complete remission is obtained. This bone marrow will later be used when a drug resistant relapse occurs, after ablative chemotherapy or total body irradiation.

Some other patients will also be treated immediately, while in complete remission, by the same ablative chemotherapy regimen, followed by autologous bone narrow transplantation, in an effort to increase tumor cytoreduction and prolong the duration of the remission as well as hopefully the overall survival.

Preliminary data have been published in: Blood Cells (in press), 1978; Blood (51, 257-265, 1978) Lancet (May 14, 1977, p. 1050); Nouvelle Presse Medicale (September 24, 1977, 6, no.31, 2741-2745); Eur. J. Cancer (submitted for publication, 1978).

42. ALLOGENEIC AND AUTOLOGOUS BONE MARROW TRANSPLANTATION AS RADICAL AND SUPPORTIVE TREATMENT OF MALIGNANCIES

Torlontano, G., Iacone, A., Di Bartolomeo, P., Fioritoni, G., Muzii, G., Geraci, L., D'Antonio, D., Di Girolamo, G., Barboni, F., Tabacchi, P. L., Beltrandi, E., University of Chieti, Istituto di Ematologia, Ospedale Civile, *Via Paolini 1, 65100 Pescara, Italy*

At present the preliminary objective of this Unit is to avoid the use of marrow transplantation (MT) in refractory leukemia (results are usually disappointing) and to consider MT only for use in treating acute leukemias in remission. In the case of the latter, it seems possible to obtain a 'cure' of patients who have undergone MT. For this purpose, three approaches have been considered: 1) Experimental programs of chemotherapy in order to obtain the highest percentage of complete remissions; 2) study of a more efficient protective environment for the patients who are to undergo transplantation; 3) studies of improved methods for yield of granulocytes useful in the case of infections resistant to antibiotic therapy.

43. ADULT LEUKEMIA CENTER - MARROW TRANSPLANTATION

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This is part of a broader project. A summary of this subproject is not available.

44. ALLOGENIC MARROW GRAFTING FOR TREATMENT OF CHRONIC MYELOGENOUS LEUKEMIA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

45. TREATMENT OF ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

Appelbaum, F. R., Fefer, A., Buckner, C. D., Thomas, E. D., Cheever, M. A., Greenberg, P. D., University of Washington, School of Medicine, Dept. of Medicine, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington,* 98195, United States of America

The objectives of the study are: 1) to determine the complete remission rate with intensive induction in adults with acute lymphoblastic leukemia; 2) to determine the overall survival of patients treated with intensive consolidation and maintenance therapy; and 3) to determine the remission duration and overall survival of patients treated with Cytoxan and total body irradiation and an HLA-matched sibling bone marrow transplant while in first remission and to compare the results with those obtained in patients who achieve a remission and are continued on chemotherapy. The approach of this study will be to treat adults with acute lymphoblastic leukemia with intensive induction therapy including vincristine, prednisone, L-asparaginase, and daunomycin. Patients achieving a complete remission who have HLA-matched siblings will be offered bone marrow transplantation while in the first remission. Those patients who lack HLA-matched siblings or who decide against a bone marrow transplant will be treated with intensive maintenance therapy. Maintenance therapy will include CNS prophylaxis and cyclical therapy with vincristine, prednisone, daunomycin, 6-mercaptopurine, and methotrexate. The number of patients entered in this study to date is too small to allow drawing any firm conclusions.

46. AUTOLOGOUS MARROW INFUSION IN CHRONIC GRANULOCYTIC LEUKEMIA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

47. BONE MARROW TRANSPLANTATION FOR RELAPSED ACUTE LEUKEMIA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

48. MARROW TRANSPLANTATION IN APLASTIC ANEMIA AND LEUKEMIA

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This program project is a coordinated multidisciplinary program of clinical and basic research into the biology of marrow transplantation as manifested in patients undergoing marrow transplantation for aplastic anemia and leukemia.

The studies in progress are designed to assess the contribution of various genetic, immunologic and hematopoietic functions to engraftment, graft-vs.-host disease or increased susceptibility to infection. Immunogenetic analyses are designed to distinguish those alloantigenic systems within and outside the major histocompatibility complex which must be common to donor and host if engraftment is to be regularly achieved and severe graft-vs.-host disease evaded. Studies of hematopoietic function are principally concerned with the biological processes which enhance or limit regeneration of normal hematologic function in the transplant recipient. Similarly, studies of the process of immune reconstitution in the marrow transplant recipient are designed to determine those functions or dysfunctions of the lymphoreticular system of the host (including lymphocytes, phagocytes, and the organs in which they develop) which may limit engraftment and functional reconstitution and, conversely, those of the marrow graft which influence the development and clinical expression of graft-vs.-host disease or complicating infections.

The patients participating in these studies are individuals with aplastic anemia or leukemia who receive transplants of marrow after treatment with standardized experimental courses of radiotherapy and/or chemotherapy for cytoreduction or immunosuppression. The clinical and experimental results of these studies will then be used as a reference base for the development and selection of new therapeutic protocols for randomized trials.

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49. BONE MARROW TRANSPLANTATION IN APLASTIC ANEMIA

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This is part of a broader project. A summary of this subproject is not available.

50. ADULT LEUKEMIA RESEARCH CENTER

Thomas, E. D., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington,* 98104, United States of America

This program project grant supports a clinical and laboratory program for a 20-bed intensive care facility with emphasis on the treatment of hematologic disorders by marrow transplantation. Principle priority has been on treatment of patients with acute leukemia or aplastic anemia. Total body irradiation and/or high dose chemotherapy is utilized to condition the patient to accept the graft and to eliminate malignant cell populations. Supportive therapies include granulocyte and platelet transfusions, laminar air flow isolation, gut sterilization and sterile diets. Immunologic recovery is monitored with long-term follow up. Supporting laboratories provide information in the areas of pathology, virology, microbiology, hematology, cryobiology, cytogenetics and histocompatibility typing. Research areas include prevention and treatment of graft-versus-host disease, opportunistic infections, acceleration of immunologic recovery and prevention of recurrent leukemia, application of immunotherapy to antileukemic treatment, in vitro assays of hematopoiesis and problems dealing with transplantation between donor-recipient non-HLA indentical pairs. Data processing and biostatistic functions provide maximum utilization of information generated.

51. ALLOGENEIC MARROW TRANSPLANT IN APLASTIC ANEMIA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

52. BONE MARROW TRANSPLANTATION FOR CANCER AND APLASTIC ANEMIA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

53. CHILDREN'S CANCER RESEARCH CENTER

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The program of the Children's Cancer Research Center focuses on the special problems of pediatric oncology and seeks: 1) To devise better and more efficient treatments using clinical and laboratory studies so as to achieve best survival and lowest early and delayed complication rates. 2) To study and understand the late adversities of therapy so that they can be avoided or mitigated. 3) To identify causative factors with a view towards reducing the incidence of childhood cancer.

Integrated clinical, epidemiologic and laboratory investigations will be used to accomplish these objectives. Leukemia, neuroblastoma and other tumors and disease states of neural crest origin will be emphasized in clinical studies and those relating to the genetics, immunology, membrane biology, epidemiology and radiobiology of pediatric neoplasia. The development of minimal therapies for low risk patients and aggressive treatments, including those requiring bone marrow rescue for children at high risk, will be stressed.

The late effects of treatment will be studied, with special reference to the learning disabilities that follow cranial irradiation for leukemia and other cancers.

54. CLINICAL CANCER RESEARCH PROGRAM

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This program project renewal application seeks support for multidisciplinary clinical research projects dealing with proposals for new methods of diagnosis and treatment of cancer. The leukemia-lymphoma program has projects in autologous bone marrow transplantation, childhood ALL, studies of newly described morphologic particles, research on lymphoproliferative and myeloproliferative disorders, leukemia immunology, platelet antigens, and biochemical pharmacologic studies of new lipid soluble folate antagonists. Additional programs are described in urologic oncology, which include a range of projects from ultrastructure, culture of human cells and clinical chemotherapy through to metabolic studies of new findings of tumor induced osteomalacia, and prognostic factors in prostatic cancer. Interdisciplinary programs in lung cancer, head and neck cancer, breast cancer, malignant melanoma, and brain tumors are also presented in this application.

The central feature of this request is that we have a newly constructed facility in which multidisciplinary research can be conducted and which provides the optimal conditions for education and patient care and enables the collection of research materials for laboratory investigations. The clinical faculty has been greatly expanded and the scope of research increased accordingly.

55. CHILDREN'S CANCER STUDY GROUP

Chard, R. L., Johnson, F. L., Pendergrass, T. W., Children's Orthopedic Hospital & Medical Center, Division of Hematology & Oncology, *4800 Sand Point Way N.E., Box C-5371, Seattle, Washington,* 98105, United States of America

This proposal is for continuation of research into the natural history, treatment and epidemiology of the statistical conduct, design, collation, and publication of childhood cancer. It will continue to emphasize multimodal aspects of the Children's Cancer Study Group which has realized such excellent results in the past in Wilms' tumors and rhabdomyosarcoma and has now helped in defining acute childhood lymphocytic leukemia as more than one disease entity which requires different treatments for different groups. Also, treatment has been improved in osteogenic sarcoma and Ewing's sarcoma and, though advances are more meager, there have also been statistical improvements in survival of neuroblastoma patients. Childhood nonlymphocytic leukemia patients have also shown improved survival and the Children's Cancer Study Group has now combined in a Groupwide study to compare bone marrow transplantation in first remission to more standard conventional chemotherapy in a controlled fashion.

During the period from November, 1976 to December, 1979, 389 children with childhood cancer were seen at this institution; 182 with leukemia, 148 who were treated on study, 44 who were not on study, and 207 children with solid tumors. We have been a member of the Children's Cancer Study Group since 1959 and strong permanent referral patterns have been established. It is therefore anticipated that the patient load will continue to be stabilized and slightly increased over the next several years. A close working relationship with the adult leukemia center under Dr. E. Donnall Thomas at the Fred Hutchinson Cancer Research Center continues. This includes the exchange of professional personnel on the Fellowship level. Forty-three bone marrow transplantations on children with acute leukemia have been done at this institution from 11/1/76 to 12/1/79. Collaborative studies continue in immunology with the Fred Hutchinson Cancer Research Center, primarily through the efforts of Irwin D. Bernstein, M.D.

BIBLIOGRAPHIC REFERENCES: Bleyer, W.A., Krivit, W., Chard, R.L., Hammond, D.: Phase II study of VM-26 in acute leukemia, neuroblastoma and other refractory childhood malignancies. Cancer Treat. Rep. Vol. 63 6:977-981, 1979. Nesbit, M., Chard, R., Evans, A., Karon, M., Hammond, G.D.: Evaluation of intramuscular versus intravenous administration of L-asparaginase in childhood leukemia. Am. J. Pediatr. Hematology/Oncology Vol. 1, 1:9-13, 1979.

56. PEDIATRIC ONCOLOGY PROGRAM PROJECT

Krivit, W., Kersey, J. H., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Pediatrics, *1305 Mayo, Minneapolis, Minnesota,* 55455, United States of America

The Pediatric Oncology Program Project is an integrated grant covering clinical and preclinical studies in oncology and bone marrow transplantation. A major emphasis of this grant is related to therapeutic investigations with emphasis on marrow transplantation for the treatment of acute leukemia, non-Hodgkin's lymphoma, neuroblastoma, aplastic anemia, and for patients at high risk for kidney graft rejection. Children and adults will be treated in these studies. Emphasis is on total lymphoid irradiation and T-cell depletion of donor bone marrow to reduce the risk of development of graft versus host disease. Preclinical investigations form a major portion of this grant, complementing and interdigitating with the therapeutic studies. Included are investigations into the nature and function of committed hematopoietic marrow cells, platelet pathophysiology, cyclophosphamide metabolism, and adrenergic mechanisms in neuroblastoma. Studies of the etiology of childhood cancers will include evaluation of the role of DNA repair mechanisms and tumor viruses.

57. CHILDREN'S CANCER STUDY GROUP

Nesbit, M. E., Krivit, W., Coccia, P. F., Ramsay, N. K., O'Leary, M., Golembe, B., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Pediatrics, *1305 Mayo, Minneapolis, Minnesota,* 55455, United States of America

The specific goals of the investigators at the University of Minnesota include the following: a) the development and implementation of groupwide studies; b) pilot new approaches for the diagnosis and treatment of childhood leukemia and solid tumors which can later be applied on a larger scale in group cooperative studies; c) evaluation of new agents for the treatment of patients with refractory malignancies; d) extension of the studies of bone marrow transplantation for the treatment of hematologic malignancies; e) evaluation of the acute and chronic effects of therapy on vital organ systems; f) development and implementation of new studies of the Intergroup Ewing's Sarcoma Study Committee.

BIBLIOGRAPHIC REFERENCES: Tefft, M., Razek, A., Perez, C., Burgert, E.O., Gehan, E.A., Griffin, P., Kissane, J., Vietti, T., and Nesbit, M.: Local Control and Survival Related to Radiation Dose and Volume and to Chemotherapy in Non-Metastatic Ewing's Sarcoma of Pelvic Bones. Internat. J. Rad. Onc., In press, 1978. Ramsay, N.K.C., Brown, D.M., Nesbit, M.E., Coccia, P.F., Krivit, W. and Krutzik, S.: Autonomous Production of the Parathyroid Hormone by Lymphoblastic Leukemia Cells in Culture. J. Pediatrics. In press, 1978.

58. CLINICAL TRIALS AND OTHER CLINICAL INVESTIGATIONS

Minna, J. D., Cohen, M. H., Bunn, P. A., Ihde, D. C., Fossieck, B. E., Shackney, S. E., Gazdar, A. F., Matthews, M. J., Carney, D., Radice, P., Abrams, P. G., Alvarez, R., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Medical Oncology Branch, *c/o Washington VAMC, Washington, District of Columbia,* 20422, United States of America

This project studies new methods of evaluating and treating malignant diseases, including: lung cancer (small cell, epidermoid, adenocarcinoma and large cell carcinoma); prostate cancer; Mycosis fungoides-Sezary syndrome (cutaneous T-cell lymphomas); multiple myeloma; hepatocellular cancer, gastric; and colon carcinoma. Therapies used in phase II and III trials include: intensive combination chemotherapy; combined chemotherapy and radiotherapy (combined modality therapy); (with the Radiation Oncology Branch) and autologous bone marrow transplantation (with the Pediatric Oncology Branch). New chemotherapeutic and immunotherapeutic agents are tested in phase I trials (with the Clinical Pharmacology Branch). Clinical histopathologic correlations are made by the resident pathologists. Extensive pre- and post-treatment staging of patients to determine the natural history of disease are carried out using: fiberoptic bronchoscopy; peritoneoscopy; CAT scans, and study of tumor markers by immunoassay (in collaboration with the Frederick Cancer Center). Studies of paraneoplastic syndromes, complications of therapy, nutritional derangements, and second malignancies are also carried out. Clinical associates are trained in medical and oncology and clinical investigation.

BIBLIOGRAPHIC REFERENCES: Huberman, M., Bunn, P.A., Matthews, M.J., Gazdar, A.F., Ihde, D.C., Cohen, M.H., Minna, J.D.: Liver Involvement in the Cutaneous T-Cell Lymphomas: The Use of Percutaneous Biopsy and Peritoneoscopy. Cancer: 7: 1683-1688, 1980. Ihde, D.C., Cohen, M.H., Simms, E.B., Matthews, M.J., Bunn, P.A., Minna, J.D.: Evaluation of Response to Chemotherapy with Fiberoptic Bronchoscopy: Results in Non-Small Cell Carcinoma of the Lung. Cancer 45: 1693-1696, 1980.

59. BONE MARROW GRAFTING IN ACUTE LEUKEMIA

Starling, K. A., Baylor College of Medicine, School of Medicine, Dept. of Pediatrics, *1200 Moursund Ave., Houston, Texas,* 77025, United States of America

This is part of a broader project. A summary of this subproject is not available.

60. FURTHER DEVELOPMENT OF CLINICAL BONE MARROW TRANSPLANTATION

Speck, B., Nissen, C., Gratwohl, A., Ruggero, D., University of Basel, Dept. of Internal Medicine, Div. of Hematology, Kantonsspital, *Petersgraben 6, 4031 Basel, Switzerland*

OBJECTIVES: a) To determine if Cyclosporin A (CyA) can prevent GvH in allogeneic bone marrow transplantation for acute leukemia and aplastic anemia. b) To determine its efficacy in the treatment of chronic GvH.

APPROACH: a) All new recipients of allogeneic grafts are placed on prophylactic CyA. Its efficacy in preventing GvH and other complications is determined. Its influence on the he-

mopoietic precursor compartment and immune function is studied in vitro. b) Its therapeutic efficacy is studied in patients from previous series who are suffering from severe chronic GvH.

61. CLINICAL AND EXPERIMENTAL STUDY OF IMMUNOLOGICAL FUNCTION AND GRAFT-VERSUS-HOST DISEASE IN BONE MARROW TRANSPLANTATION

Humphrey, J. H., Gordon Smith, E. C., University of London, Royal Postgraduate Medical School, Dept. of Immunology/ Haematology, *c/o Hammersmith Hospital, Du Cane Rd., London W12 0HS, England, United Kingdom*

Patients receiving bone marrow allografts for aplastic anemia or acute leukemia, or bone marrow autografts for acute leukemia in relapse (accompanied by cytotoxic drug and/or irradiation) are monitored for development of GVH disease and for in vitro reactivities with preserved recipient lymphocytes taken before grafting. The aim is to discover whether GVH disease can be predicted, and what factors determine its onset or remission. Empirical observations are made on absorption of bacterial endotoxin from the gut, on interferon production and on various routine immunological parameters.

Mild or severe GVH is produced in allogeneic and congeneic rats subjected to bone marrow transplantation, with the aim of discovering the cells responsible for GVH disease and the efficacy of antibodies against helper and/or suppressor T-cells in preventing or curing GVH disease, and of studying the immunological effectiveness of surviving host macrophages and monocytes derived from donor bone marrow.

62. MARROW GRAFTING IN TREATMENT OF HEMATOLOGIC MALIGNANCIES

Storb, R. F., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

Over the past years the Division of Oncology at the University of Washington has been involved in a continuing program of marrow transplantation for the treatment of patients with advanced, otherwise fatal malignant and non-malignant hemopoietic diseases. A number of grafted patients have become long-term survivors without recurrence of their original disease and without occurrence of graft-versus-host disease. Many patients, however, have died from recurrent disease or, more frequently, from complications related to the transplant. Further improvement in clinical marrow grafting hinges upon progress in and better understanding of at least three major areas of study: 1) Recovery of immunologic reactivity in marrow graft recipients, 2) understanding of mechanisms of stable graft-host tolerance and of graft-versus-host disease, 3) methods of recognizing and overcoming sensitization of a marrow graft recipient by previous blood transfusions. It is the objective of this proposal to conduct an immunologic investigation into those three areas of study.

BIBLIOGRAPHIC REFERENCES: Atkinson, K., Meyers, J.D., Storb, R., Prentice, R.L. and Thomas, E.D.: Varicella-zoster virus infection after marrow transplantation for aplastic anemia or leukemia. Transplantation 29: 47-50, 1980. Ringden, O., Witherspoon, R.P., Storb, R., Ekelund, E. and Thomas, E.D.: Increased in vitro B-cell IgG secretion during acute graft-versus-host disease and infection. Observations in 50 human marrow transplant recipients. Blood 55: 179-186, 1980.

63. MECHANISM OF GVHD POST MARROW GRAFTING

Tsoi, M., Fred Hutchinson Cancer Research Center, Division of Medical Oncology, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

Marrow transplantation from HLA identical siblings has been used with increasing success for the treatment of otherwise fatal malignant and non-malignant hematological diseases. A number of patients are surviving for up to 8 years leading normal lives. Many patients, however, have died either from recurrent disease or, more frequently, from graft-versus-host disease (GVHD) and associated infectious complications. Furthermore, 20% of long-term survivors develop chronic GVHD and associated immunologic deficit. It is the objective of this proposal to investigate the mechanisms involved in acute and chronic GVHD in patients with marrow grafts.

Using two sensitive cell-mediated cytotoxicity assays we have shown marked in vitro cytotoxicity against patient fibroblasts caused by a lymphocyte subpopulation in acute GVHD patients. On the other hand, we have demonstrated nonspecific suppressor activity of mononuclear leukocytes in chronic GVHD patients, inhibiting donor lymphocyte response in the blastogenesis assay. Long-term stable survivors, however, have neither specific cytotoxicity nor nonspecific suppressor activities. We propose to study the effector mechanism of acute GVHD and also the suppressor mechanism in chronic GVHD. Sequential and comparative studies will be undertaken to understand the relationship of these cells to acute and chronic GVHD. Special effort will be devoted to the isolation of the cytotoxic and the suppressor cells. While the former cells may be isolated by immunoabsorption on antigen-specific fibroblasts, both cell populations may be isolated by various column chromatography, selective rosetting, determination of density gradient and sedimentation velocity methods. These cells will be characterized on the basis of surface marker properties. Soluble suppressor factors, if present, will be isolated and characterized by biochemical methods. The possibility of producing heteroantisera against the purified cells and soluble suppressor factor will be considered.

64. APPLICATION OF AUTOLOGOUS BONE MARROW TRANSPLANTATION IN TREATMENT OF PATIENTS WITH MALIGNANT TUMORS AND CML

Bucher, U., Beck, E. A., Odavic, R., Inselspital, Dept. of Hematology, *CH3010 Bern, Switzerland*

OBJECTIVE: The objective of the research project is the evaluation of the adjuvant therapy involving transplantation of autologous bone marrow in treatment of patients with solid tumors or CML in acute blastic transformation.

APPROACH: Hemopoietic stem cells are collected from patients with solid tumors without involvement of the bone marrow, separated from the bulk of mature cells by density gradient centrifugation and cryopreserved. After intensive chemotherapy and radiotherapy the aplastic patient is rescued by reinfusion of autologous marrow and cell support. In a group of patients with CML, stem cells from bone marrow and peripheral blood collected by aspiration or by an Aminco cell separator, respectively, are splenectomized. In the blastic transformation phase intensive chemotherapy and radiotherapy will be applied with reinfusion of stored stem cells with the aim of reverting patient's disease into the chronic phase.

PROGRESS: During four years the process of cell separation and cryopreservation was tested on more than 100 normal bone marrows. A standardization of the CFU-c assay was attempted by the use of cryopreserved stimulating and target cells. This assay was used for the evaluation of the proliferation potential of frozen stem cells. A mixture of Dextran and DMSO was found to be equivalent to DMSO alone in cryoprotection of human CFU-c.

65. BONE MARROW TRANSPLANTATION IN HUMAN DISEASE

Santos, G. W., Johns Hopkins University, School of Medicine, Dept. of Medicine, *725 N. Wolfe St., Baltimore, Maryland*, 21205, United States of America

The purpose of this program project grant is to investigate the immunobiology and improve the therapeutic effects of syngeneic, autologous, and allogeneic marrow transplantation in clinical malignancy and in disease involving bone marrow failure. The proposal is made up of five projects: (1) Therapeutic Application of Marrow Transplantation and Supportive Program Services; (2) Immunogenetics as Applied to Clinical Bone Marrow Transplantation; (3) Graft-Versus-Host Reaction and Disease (GVHD); (4) Autologous Lympho-hematopoietic Transplantation and (5) Radiotherapy as Applied to Lympho-hematopoietic Transplantation. The objectives of the various projects are: (1) Explore the therapeutic potential of cytoreductive treatment combined with syngeneic, autologous, and allogeneic marrow transplantation in human malignancy and aplastic anemia; (2) identify and characterize non-HLA and HLA-linked factors that are pertinent to engraftment and GVHD; (3) examine in depth the nature, prediction, prevention and treatment of GVHD; (4) further develop the methodology and study the effects of autologous lympho-hematopoietic transplantation in malignancy and (5) study the effects of fractionated radiotherapy together with chemotherapy in preclinical models.

66. IMMUNOLOGIC STUDIES IN MARROW TRANSPLANTATION (HUMAN)

Storb, R. F., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This is part of a broader project. A summary of this subproject is not available.

67. RECONSTITUTION OF IMMUNOLOGIC REACTIVITY IN MARROW GRAFT RECIPIENTS

Storb, R. F., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This is part of a broader project. A summary of this subproject is not available.

68. IMMUNOLOGIC REACTIVITY OF MARROW TRANSPLANT RECIPIENTS (HUMAN)

Thomas, E. D., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This is part of a broader project. A summary of this subproject is not available.

69. BONE NARROW TRANSPLANTATION, MALIGNANCIES AND IMMUNE DEFICIENCIES (HUMAN)

Humphrey, G. B., University of Oklahoma, Health Science Center, School of Medicine, Dept. of Pediatrics, *Box 26901, Oklahoma City, Oklahoma*, 73190, United States of America

This is part of a broader project. A summary of this subproject is not available.

70. IMPORTANCE OF GRANULOCYTE ANTIGENS IN LEUCOCYTE TRANSFUSIONS AND BONE-MARROW TRANSPLANTATIONS

Jeannet, M., Cruchaud, A., vonFliedner, W., Hopital Cantonal, Transplantation Immunology Unit, *64 Ave. de la Roseraie, 1211 Geneva 4, Switzerland*

OBJECTIVE: To study the importance of granulocyte antigens to the survival of transfused white blood cells in vivo in immunized patients and also to the 'take' of bone-marrow transplants.

APPROACH: Granulocyte antibodies will be sought in the sera of patients receiving multiple granulocyte transfusions or a bone-marrow transplant using several techniques (leucoagglutination granulocytotoxicity, ADCC, immunofluorescence). Crossmatch tests will be performed using donor granulocytes and recipient serum with the same techniques. The effect of granulocyte antibodies on the in vivo survival of granulocytes after transfusions and on the take of bone marrow cells after transplantation will be assessed. Eventually donors and recipients will be typed for the few granulocyte antigens known at the present time.

71. PHAGOCYTIC FUNCTION IN MARROW TRANSPLANT

Smithwick, E. M., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

72. HEMATOPOIETIC STEM CELL FUNCTION IN BONE MARROW RECIPIENTS

Moore, M. A., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

73. EVALUATION OF B-CELL FUNCTION IN BONE MARROW TRANSPLANT RECIPIENTS

Pahwa, S., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

74. MODULATION OF T-CELL ACTIVITY AFTER BONE MARROW TRANSPLANTATION

Gupta, S., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

75. TOTAL BODY IRRADIATION FOR BONE MARROW TRANSPLANT

Kim, T. M., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Therapeutic Radiology, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

This is part of a broader project. A summary of this subproject is not available.

76. NAVY ENVIRONMENT - TREATMENT OF RADIATION CASUALTIES WITH BONE MARROW TRANSPLANTATION

Romano, P. J., Georgetown University, School of Medicine, Dept. of Pediatrics, *3800 Reservoir Rd. N.W., Washington, District of Columbia*, 20007, United States of America

This research to define homozygous typing white blood cells is to provide a practical test for successful bone marrow transplantation treatment of radiation casualties. The work is concerned with the specificity of antigens which are responsible for producing mixed lymphocyte culture responses.

The presence of LD homozygocity will be determined in blood obtained from subjects known to have close genetic association. Cells typed for all known HLA-A, -B and -C antigens will be used in tests with homozygous cells to establish D specificities. Purified lymphocytes obtained from leukapheresed cells using standard techniques are to be frozen for later tissue typing. The typing is required to ensure that all known A, B and C specifications are identified and a complete test panel is available for evaluation of LD cells.

77. AUTOLOGOUS MARROW TRANSPLANTATION FOR CANCER THERAPY

Herzig, G. P., Phillips, G. L., Wolff, S. N., Washington University, School of Medicine, Dept. of Internal Medicine, *660 S. Euclid Ave., St. Louis, Missouri*, 63110, United States of America

Patients with advanced malignancy refractory to conventional therapy will undergo cryopreservation of their own histologically normal bone marrow for use later to protect against potentially lethal myelosuppression due to intensive chemotherapy or radiotherapy. Marrow will be preserved by controlled rate freezing with dimethylsulfoxide and will be stored in liquid nitrogen. Patients with malignant lymphoma will be treated with cyclophosphamide and supralethal (1000 rads) total body irradiation followed by infusion of their own cryopreserved marrow. In preliminary studies 2/5 patients have achieved prolonged (10 plus and 16 plus months) unmaintained remissions and treatment of additional patients will establish the true response rate. Other studies are designed to evaluate individual chemotherapy agents at doses which have not been possible previously because of myelosuppression. Drug doses will be escalated in successive patients beginning at the highest conventional dose and continuing until some new life-threatening toxicity appears. When the maximum safe dose (with autologous marrow transplantation) has been established, additional patients will be evaluated for tumor response. In a pilot study with Bischloroethyl-nitrosourea (BCNU), a 3-fold increase in BCNU dose has been achieved without fatal drug related toxicity, and 5/8 patients with measurable disease have shown objective tumor responses. Additional patients will be required to establish the maximum tolerable dose and anti-tumor effect. With completion of the BCNU studies, other agents will be evaluated in a similar fashion, and finally combinations of these agents will be studied based on their demonstrated anti-tumor activities and toxicities. Ancillary studies are designed to determine the ability of cryopreserved autologous marrow to reconstitute immune function and to examine in vitro assays for hematopoietic stem cells to determine whether a relationship between these assays and the ability of cryopreserved marrow to restore hematopoiesis exists. The demonstration of such a relationship would permit use of the assay to optimize freezing and storage techniques and to ensure the viability of marrow prior to transplantation.

78. REGULATION OF GRANULOPOIESIS IN NORMAL AND ABNORMAL STATES

Mahmood, T., Robinson, W. A., Wallner, S. F., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *1055 Clermont St., Denver, Colorado*, 80210, United States of America

RESULTS: We recently reported on six patients with anemia, thrombocytosis, unilobate megakaryocytes and deletion of long arm of chromosome No. 5, termed 5q-syndrome. We have examined the proliferative capacity of the bone-marrow growth in vitro in three of these patients. Our in vitro data suggests that this syndrome is not pre-leukemic in nature. None of these patients has turned leukemic in a follow-up of up to 5 years (American Journal of Medicine 66:946, 1979).

We recently reported on the technique of cryopreservation of bone marrow from normal subjects, patients with chronic myelogenous leukemia and patients with acute leukemia. Our studies suggest that long term preservation of human bone marrow is possible (Exp. Hemat. 7:321, 1979). We also reported on the use of this cryopreserved bone marrow for the treatment of patients with chronic myelogenous leukemia in blast crisis and myelofibrosis. (Exp. Hemat. 7:27, 1979). One patient had reversal of severe myelofibrosis as documented by silver stain. Future course: Cryopreservation of bone marrow from 20 more patients with CML will be carried out. At least another 5-8 patients are expected to undergo blast crisis and will require autologous bone marrow infusion along with high dose chemotherapy.

Characterization of factors produced by human T lymphocytes and T cell lines is also under way. The modulation of the production of these factors in mixed lymphocyte culture is also being studied.

79. USE OF AUTOLOGOUS CRYOPRESERVED MARROW AND PERIPHERAL BLOOD STEM CELLS IN PROTECTION AGAINST LETHAL CHEMOTHERAPY IN CANCER TREATMENT

Herrmann, R. P., Davis, R. E., Sliwowska, N., Royal Perth Hospital, Dept. of Haematology, *Wellington St., Perth, Western Australia, Australia*

OBJECTIVE: There are two objectives to this project. Firstly to obtain peripheral blood and bone marrow stem cells which are capable of repopulating the patient's marrow after cryopreservation and reinfusion. Secondly to remove immunologically small numbers of leukemic blast cells from the obtained peripheral blood and marrow.

APPROACH: Peripheral blood stem cell collections (assayed by DFU-C) are obtained in patients with acute lymphoblastic leukemia, acute myeloid leukemia and chronic myeloid leukemia. The stem cells in acute leukemia are obtained at intervals following reinduction cycles of chemotherapy when the stem cells are circulating in significant numbers in the peripheral blood. Bone marrow is also harvested when the disease is in remission. It is planned to use the cryopreserved material in patients following intensive chemotherapy after relapse of the disease.

In patients newly presenting, leukemic cells are collected from peripheral blood and marrow and cryopreserved in aliquots. Rabbits are being immunized with these cells together with either Freund's adjuvant or BCG. It is then proposed to adsorb the antisera produced and demonstrate their antileukemic activity by inhibition of growth in liquid culture of the previously obtained leukemic cells. It is then proposed to add the adsorbed antiserum to agar colony cultures of the patient's remission bone marrow and attempt to demonstrate that the antiserum does not inhibit normal CFU-C GM formation.

80. AUTOLOGOUS BONE MARROW RECONSTITUTION AND EXTENDED CHEMOTHERAPY IN HUMAN CANCER

Epstein, R. B., Sarpel, S. C., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *820 S. Damen Ave., Chicago, Illinois*, 60612, United States of America

The present proposal is directed at initiating a pilot trial of the use of cryopreserved autologous hematopoietic stem cells for reinfusion following intensive chemotherapy for the treatment of human neoplasms. Patients selected for the study will include: a) Adults with acute myelogenous leukemia during their first remission following standard chemotherapeutic regimens, b) patients with chronic granulocytic leukemia during the early phase of control, c) patients with small cell and inoperable large cell carcinoma of the lung clinically limited to areas above the diaphragm, d) selected patients with other solid tumors with no demonstrable evidence of bone marrow involvement who fail to respond to a standard chemotherapeutic regimen. Hematopoietic cells will be procured by the multiple marrow aspiration technique under general or spinal anesthesia. Quantities for infusion should exceed 2 times 10 to the eighth power per kg of body weight. If these numbers are not reached, supplemental peripheral blood hematopoietic stem cells will be obtained by leukapheresis techniques. Cryopreservation of procured cells will be carried out using dimethyl sulfoxide as the cryopreservative and a programmed freezing rate. At the onset of initial leukemic or visceral tumor relapse, intensive chemotherapy protocols will be initiated followed by the infusion of the cryopreserved marrow. Patients will be evaluated in terms of the ability of infused marrow to provide for prompt hematopoietic recovery and for measurable tumor responses. In addition, in vitro assays of granulocyte colony forming units will be performed serially to measure the potential of the assay in monitoring the effect of autologous reinfusion.

81. GI MUCOSA AFTER CANCER CHEMOTHERAPY AND BONE MARROW TRANSPLANTATION

Parkman, R., Children's Hospital Medical Center, *300 Longwood Ave., Boston, Massachusetts*, 02115, United States of America

This is part of a broader project. A summary of this subproject is not available.

82. TREATMENT OF METASTATIC BREAST CANCER WITH COMBINATION CHEMOTHERAPY AND BONE MARROW INFUSION

Herzig, G. P., Washington University, School of Medicine, Dept. of Internal Medicine, *660 S. Euclid Ave., St. Louis, Missouri*, 63110, United States of America

This is part of a broader project. A summary of this subproject is not available.

83. TREATMENT OF OVARIAN CANCER WITH COMBINATION CHEMOTHERAPY AND BONE MARROW INFUSION

Herzig, G. P., Washington University, School of Medicine, Dept. of Internal Medicine, *660 S. Euclid Ave., St. Louis, Missouri*, 63110, United States of America

This is part of a broader project. A summary of this subproject is not available.

84. TRANSPLANTATION OF BONE MARROW, FETAL LIVER OR THYMUS

O'Reilly, R. J., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

85. AUTOLOGOUS MARROW RESCUE AFTER INTENSIVE CHEMOTHERAPY

Robinson, W. A., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Medicine, *4200 E. 9th Ave., Denver, Colorado*, 80262, United States of America

The aim of this study is to determine if autologous bone marrow removal and infusion is beneficial and can lead to earlier hematopoietic recovery and more effective treatment in humans receiving intensive chemotherapy for neoplastic disease. In the initial studies proposed patients with neoplastic disease refractory to conventional therapy will have large amounts of marrow removed, stored whole at 4 degrees C, and reinfused 48 hours later after 36 hours of intensive standardized chemotherapy. Control patients will have the same chemotherapy and marrow removal, but the marrow will be cryopreserved and reinfused only if recovery of hematopoiesis is delayed. Recovery of hematopoietic function in these two groups will be studied and compared using standard hematologic parameters and measurement of blood and marrow colony forming units in culture. Concomitant in vitro studies will be done to determine the best methods of storage for preservation of viability and function of both mature and immature cells in the marrow. The findings will be incorporated into subsequent in vivo studies

during the second phase of the program. Finally, if it can be shown that autologous bone marrow infusion is beneficial in humans when a standard chemotherapy regimen is used, studies will be done to develop specific chemotherapy and marrow infusion programs for individual neoplastic diseases.

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86. ABLATIVE THERAPY FOLLOWED BY AUTOLOGOUS HEMATOPOIETIC RECONSTITUTION FOR SMALL CELL CARCINOMA OF THE LUNG IN REMISSION (ABBREV)

Ihde, D. C., Bunn, P. A., Minna, J. D., Cohen, M. H., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Medical Oncology Section, *50 Irving St. N.W., Washington, District of Columbia,* 20422, United States of America

Therapy: 1) Collect autologous bone marrow after 12 weeks of CAPO (NCI-VA MOB 77-3). 2) CTX 60 mg/kg plus VP-16 200 mg/m2 IV qd x 2, then TBI 400 rad qd x 2. 3) Reconstitute with autologous bone marrow plus two infusions of previously collected autologous peripheral blood buffy coat.

Number of patients entered: none.

Future plans: begin patient accrual as soon as patients with complete responses to CAPO therapy are accumulated.

87. BCNU THERAPY AND MARROW AUTOGRAFT FOR UNRESPONSIVE MALIGNANCY (HUMAN)

Herzig, G., Washington University, School of Medicine, Dept. of Internal Medicine, *660 S. Euclid Ave., St. Louis, Missouri,* 63110, United States of America

This is part of a broader project. A summary of this subproject is not available.

88. HEMATOLOGICAL SUPPORT OF PATIENTS WITH CANCER

Deisseroth, A., Abrams, R., Ihde, D., Bowles, J. C., Glaubiger, D., Terasaki, P., Minna, J., Glatstein, E., Trapani, R., Phillips, T., Wright, D., Cohen, M., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Experimental Hematology Section, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

Hematopoietic reconstitution using autologous marrow cells is being evaluated as an adjunct to trials of intensive therapy in resistant sarcomas, small cell carcinoma of the lung, and undifferentiated lymphoma. Pharmacologic amplification of peripheral blood levels of autologous stem cells is being studied as a means of accelerating both immunological and myeloid recovery following intensive therapy in man and in a canine model. Studies of the interaction of autologous peripheral blood and marrow stem cell infusions during reconstitution is being conducted in an animal model. Studies in vitro and clinical trials are undertaken to define the optimal platelet support of cancer patients. Extracorporeal hemoperfusion through immunoadsorbent columns, using continuous flow centrifugation in a canine model and in clinical trials, is being studied as a means of inducing regression in tumors resistant to established forms of therapy. Finally, extensive in vivo studies of changes in immune complexes, suppressor cell activity, and various arms of the cellular immune response are being pursued in an attempt to elucidate the mechanism of tumor regression seen following immunoadsorbent therapy.

BIBLIOGRAPHIC REFERENCES: Abrams, R., Glaubiger, D., Simon, R., Lichter, A., and Deisseroth, A.: Four week reduction of myelosuppression by autologous stem cell infusions in man. The Lancet, in press, 1980. Tosato, G., Appelbaum, F.R., Trapani, R.J., Dowling, R., and Deisseroth, A.B.: Use of 'in vitro' assays in selection of compatible platelet donors. Transfusion 20: 47-54, 1980.

89. HIGH DOSE DMM THERAPY WITH AUTOLOGOUS MARROW INFUSION

Buckner, C. D., Thomas, E. D., Storb, R., Fefer, A., Neiman, P., Slichter, S. J., Glucksberg, H., Goodell, B., Weiden, P. L., Sanders, J., Cheever, M. A., Fred Hutchinson Cancer Research Center, Division of Oncology, *1124 Columbia St., Seattle, Washington,* 98104, United States of America

This project is a phase I and II study to ascertain the maximum tolerable single dose of dimethyl myleran that can be given with autologous marrow rescue and to evaluate the therapeutic response and survival in a variety of malignancies resistant to conventional therapy.

Dimethyl myleran is an alkylating agent that is not phase or cycle dependent and the effect of which is independent of the proliferative state. There are very few chemotherapeutic drugs that fall into the category of class I (proliferative rate independent) cytotoxic agents. Animal studies have shown that syngeneic marrow will protect from otherwise lethal doses. However, clinical trials have been limited due to its marrow toxicity. Non-marrow toxicity in animal studies consists exclusively of mucositis and diarrhea. Interest in the drug is heightened by its relative lack of immunosuppressive properties.

90. CONFERENCE ON AUTOLOGOUS BONE MARROW TRANSPLANTATION

Robinson, W. A., Mangalik, A., Weiner, R. S., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Medicine, *4200 E. 9th Ave., Denver, Colorado,* 80262, United States of America

One of the major limitations in the management of a number of endoplasms with high dose chemotherapy is bone marrow suppression. Autologous bone marrow transplantation is a method which may allow the use of high dose chemotherapy with reduced bone marrow toxicity. In order to best utilize the potential of autologous bone marrow transplantation, workers from many areas need to exchange the currently available information. Cryobiology, immunology, experimental therapeutics, radiation biology, experimental hematology, oncology, radiation therapy, and clinical hematology are some of the areas that need to be coordinated for the best results of this form of treatment. The planned symposium will bring together experts from these different specialties who have, in many cases, been involved with studies on human bone marrow cells. It is expected that better studies on this modality of treatment can be initiated based on the new information generated at this meeting.

91. STORED AUTOLOGOUS MARROW IN THE THERAPY

Thomas, E. D., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington,* 98104, United States of America

This is part of a broader project. A summary of this subproject is not available.

92. ALLOGENIC BONE MARROW TRANSPLANTATION (HUMAN)

Gale, R. P., University of California, Los Angeles Campus, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California,* 90024, United States of America

This is part of a broader project. A summary of this subproject is not available.

93. STORAGE AND AUTOLOGOUS TRANSPLANTATION OF HUMAN BONE MARROW

Graze, P., University of California, Los Angeles Campus, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California,* 90024, United States of America

This is part of a broader project. A summary of this subproject is not available.

94. BONE MARROW TRANSPLANTATION (HUMAN)

Graze, P. R., University of California, Los Angeles Campus, School of Medicine, Dept. of Microbiology & Immunology, *2025 Zonal Ave., Los Angeles, California,* 90024, United States of America

This is part of a broader project. A summary of this subproject is not available.

95. AUTOLOGOUS BONE MARROW TRANSPLANTATION AND RESCUE (HUMAN)

Robinson, W. A., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Medicine, *4200 E. 9th Ave., Denver, Colorado,* 80262, United States of America

This is part of a broader project. A summary of this subproject is not available.

96. AUTOLOGOUS MARROW TRANSPLANTATION

Buckner, C. D., Thomas, E. D., Stewart, P., Bensinger, W., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

We propose to evaluate the effectiveness of high dose chemoradiotherapy in a variety of malignant diseases including acute leukemia, chronic granulocytic leukemia, oat cell carcinoma, malignant lymphoma, ovarian carcinoma, breast carcinoma and resistant pediatric solid tumors. Patients will have marrow cryopreserved prior to therapy and reinfused following intensive therapy with regimens developed in the syngeneic and allogeneic transplant programs. The effectiveness of this approach in terms of marrow repopulation and therapeutic effectiveness will be evaluated.

97. BONE MARROW TRANSPLANTATION

Parkman, R., Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts*, 02115, United States of America

This is part of a broader project. A summary of this subproject is not available.

2. EXPERIMENTAL BONE MARROW TRANSPLANTATION

98. CANCER CHEMOTHERAPY OF HUMAN TUMORS GROWN IN IMMUNOSUPPRESSED MICE WITH DIMETHYL MYLERAN AND MARROW RESCUE

Floersheim, G. L., Zentrum f. Lehre u. Forschung, Kantonsspital Basel, *Hebelstrasse 20, 4031 Basel, Switzerland*

OBJECTIVE: To test the sensitivity of human tumors grown in immunosuppressed mice to superdosis chemotherapy with dimethyl myleran followed by bone marrow transplantation.

APPROACH: In contrast to our previous project, human tumors are now grown in conventional immunosuppressed mice. For this purpose, male C3H mice are treated on days -3 and -1 simultaneously with 45 mg/kg cyclophosphamide s.c. and 135 mg/kg procarbazine s.c. and on days -2 and 0 with 0.15 ml/10 g antithymocyte serum (ATS) s.c. On day 0, fragments of human tumors are transplanted subcutaneously to these mice. A colon carcinoma, a bronchogenic carcinoma, a Ewing sarcoma and two osteosarcomas grew satisfactorily with a take rate approaching 100 percent. Large, cherry-sized tumors persist or progress in about 50 percent of the mice while the remaining tumors begin to regress after 3 or 4 weeks. While nude mice, which need no conditioning, may remain for practical reasons more convenient to receive de novo implantations of primary tumor biopsies, the subsequent tumor transfer to immunosuppressed mice would take advantage of their better survival and economy, allowing both large scale screening of chemotherapeutic agents against human tumors and the testing of individual clinical cancers for their sensitivity to cancer chemotherapy. Our plan is to test which human tumors can be eradicated with superdosis chemotherapy with dimethyl myleran followed by autologous or isologous marrow rescue.

PROGRESS: The method for growing human tumors in conventional mice after short-term synergistic immunosuppression has been published (Floersheim, G.L., Nassenstein, D. and Torhorst, J.: Transplantation, 30, 275-280, 1980).

99. CHRONIC GRAFT-VERSUS-HOST DISEASE IN THE RAT RADIATION CHIMERA

Beschorner, W. E., Tutschka, P. J., Johns Hopkins University, School of Medicine, Dept. of Pathology, *725 N. Wolfe St., Baltimore, Maryland*, 21205, United States of America

Chronic graft-versus-host disease (GVHD) is a frequent and often fatal sequela of human allogeneic bone marrow transplantation with features of scleroderma, Sjogren's syndrome and chronic active hepatitis. We have observed a very similar disease developing spontaneously in rat radiation chimeras. We have been able to induce chronic GVHD rapidly and consistently by two alternative methods: sublethal irradiation of chimeras followed by a booster bone marrow transplant and by adoptive transfer of chimera marrow and lymphocytes into third party irradiated recipients. Histology reveals dense dermal collagenosis, lymphoplasmacytic infiltrate and injury of the salivary and lacrimal gland ducts and chronic hepatitis with bile injury. Preliminary immunopathological studies suggest the presence of both allogeneic and organ specific antibodies.

This model has excellent potential for the study of the pathogenesis of chronic GVHD, a preclinical model for modes of therapy and prevention of chronic GVHD, and of probable value for studying some autoimmune disorders. We plan to thoroughly characterize the histopathology, distinguishing the disease from effects of aging, irradiation and infections. Immunopathological characterization will include definition of humoral and cellular components, antigen specificity of acid eluates of target organs and separation of the reactions against histocompatability antigens for reaction against organ specific antigens.

100. TOLERANCE OF BONE MARROW GRAFTS

Click, R. E., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Microbiology, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

The overall objective of our grant is to define the effect of genetic and environmental factors on the survival time of x-irradiated mice undergoing graft-vs-host (GVH) after reconstitution with H-2 disparite bone marrow cells. One aim was to establish the number of independently segregating genes which controlled products previously assigned to the presumed single gene, Mls. Clarification of the ambiguities of Mls is an important point in our studies of the suspected ability of Mls products to modulate GVH induced by H-2 disparite cells.

BIBLIOGRAPHIC REFERENCES: Click, R. E., Tolerance of histoincompatible marrow grafts, Transplant. Proc. 11: 490, 1979.

101. IMMUNOGENETIC AND OTHER FACTORS AFFECTING BONE MARROW TRANSPLANTATION IN IRRADIATED MICE

Uphoff, D. E., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Radiation Biology Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

Results of our studies demonstrate, for the first time, that biological systems are affected by qualitative differences in X-irradiation. The evidence includes differences in the 30 day LD 50 values and differences in the slope of the mortality curves. Differences in dorsal, ventral and two-directional exposures delivered simultaneously at half the dose rate were characterized and related to the relative uniformity of the dose to the bone marrow. The protective effect of anesthesia during irradiation was studied in relation to recovery time and the reduction of oxygen tension in the bone marrow.

102. LEUKEMIC AND STEM CELL MONOCLONAL ANTIBODIES

Dicke, K. A., Lafferty, M. D., Zander, A. R., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Developmental Therapeutics, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

Monoclonal antibodies to human hemopoietic precursor cell and/or leukemic cell antigens will be raised using a mouse-mouse cell hybridoma technique. Human brain, null ALL cells and light density CML cells will be used as immunogens. Supernatants from the hybridoma clones will be tested for the presence of antibodies and the antibody specificities using an ELISA (enzyme-linked immunosorbant assay) and a modified ELISA. In the modified ELISA, normal hemopoietic precursor cells, null ALL cells, CML cells and normal peripheral blood cells will be used as targets. Selected clones will be cultured for the production of large quantities of monoclonal antibodies. These atibodies will be tested for their reactivity to normal hemopoietic precursor cells using the following in vitro assays: CFC-GM (colony-forming cells - granulocyte, macrophage), BFU-E (burst-forming units - erythroid) and Dexter suspension cultures (long-term surviving hemopoietic precursors). The reactivity of the antibodies to the leukemic populations of ALL, AUL, AML, AMML, CLL, CML and CML-BC will be tested by various immunologic techniques (complement fixation, modified ELISA and immunofluorescence). The quality of antibody bound to various normal and leukemic cell types will be done using a FACS (fluorescence-activated cell sorter). These studies will determine if the monoclonal antibodies can be used to separate leukemic cell populations from normal hemopoietic precursor cell populations. Preparative, highly selective separa-

tion methodology can then be developed for use in our autologous bone marrow transplantation program.

BIBLIOGRAPHIC REFERENCES: Vellekoop, L., Thomson, S., Stewart, D., Zander, A.R., Spitzer, G., Verma, D.S., Lafferty, M. and Dicke, K.A.: Separation of human leukemic cells and normal hemopoietic stem cells by density centrifugation on a discontinuous albumin gradient. Experimental Hematology, Volume 7, Supplement No. 6, p. 101, 1979. Dicke, K.A., Zander, A.R., Spitzer, G., Verma, D.S., Peters, L., Vellekoop, L. and McCredie, K.B.: Autologous bone marrow transplantation: Adult acute leukemia in relapse. The Lancet, I(8115):514-517, 1979.

103. PRECLINICAL ANIMAL BONE MARROW TRANSPLANTATION

Bowles, C. A., Hazleton Lab. America Inc., *9200 Leesburg Tpke., Vienna, Virginia*, 22180, United States of America

OBJECTIVE: Provide technical and support services to perform granulocyte transplantation and immunotherapy studies for which protocols will be provided by the NCI. The veterinary and scientific investigators will meet on a weekly basis with the Experimental Hematology Section staff and discuss the formulation of experiments in maintenance and analysis of data arriving from outgoing protocols. Daily deliveries to and from the NIH, Building 10, and communication with the Experimental Hematology Section are required.

104. IRRADIATION AND MARROW TRANSPLANTATION IN LARGE ANIMALS

Thomas, E. D., University of Washington, School of Medicine, Dept. of Medicine, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington*, 98195, United States of America

OBJECTIVE: To study marrow transplantation biology and immunology in large outbred animals, primarily the dog.

APPROACH: This is a continuing study of total body irradiation (TBI) and marrow transplantation, high dose chemotherapy and marrow transplantation, methods of support for animals that have no bone marrow function, and the immunologic problems of marrow transplantation. Specific areas of study include the immuno-reactivity of canine marrow transplant recipients, the nature of the tolerance observed in the healthy long-term canine chimeras, the effect on engraftment of preceding exposure to transplantation antigens by blood transfusion, the prevention and treatment of graft-vs-host-disease (GVHD), the problems of histocompatibility typing, and studies of the immunologic problems arising from long-term support by platelet and granulocyte transfusions.

PROGRESS: We have shown that canine radiation chimeras have a significant immunologic deficiency for the first 200 days post-transplantation but that long-term radiation chimeras are relatively intact immunologically. We have shown that the stable chimeric state cannot be ascribed to the presence of serum blocking activity at least as measured in vitro by the microcytotoxicity (cell inhibition) assay. We have shown in unrelated dogs that prior exposure to donor transfusions can prevent successful engraftment but that this pre-sensitization can be overcome by a regimen of antithymocyte serum and procarbazine. Additional studies on the effects of transfusion prior to marrow grafting indicated that exposure to donor blood from 24 hours to 3 months before marrow grafting significantly increased the likelihood of graft rejection. We have established the utility of methotrexate in ameliorating GVHD and the effectiveness of antithymocyte serum in treating established GVHD. Studies using the mixed leukocyte culture and the cell-mediated lympholysis assay have established that one or more additional loci other than the lymphocyte-defined and serum-defined loci are important for the outcome of a marrow graft.

105. EFFECT OF CHEMOTHERAPY ON BONE MARROW TRANSPLANTATION - AN IN VITRO STUDY

Canellos, G. P., Greenberger, J., Cohen, G. I., Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts*, 02115, United States of America

Methods currently available to prepare a tumor bearing host for bone marrow transplantation include total body irradiation and systemic high dose chemotherapy. Engraftment is often delayed with the slow return of the platelet count, often depressed for weeks, requiring transfusional support in patients. A possible mechanism for the failure of successful bone marrow engraftment may be related to the effects of chemotherapy on bone marrow stromal cells resulting in a suboptimal milieu for the reinitiation of hemopoiesis.

A unique long-term bone marrow liquid culture system which demonstrates absolute dependence upon corticosteroid for sustained hemopoietic stem cell proliferation has now been described. By a modification of the method originally described by T.M. Dexter, we can produce a culture which permits the growth of stromal elements only. Engraftment of non-adherent cells containing CFUc and CFUs onto stromal cultures results in islands of hemopoietic cell growth which are maintained for more than 10 weeks. We plan to investigate the role of the bone marrow stroma in the support of hemopoietic stem cell proliferation. The effect of chemotherapeutic agents currently in use in autologous marrow transplantation will be studied to determine what effect, if any, these agents have on the stromal cells of recipients of allogeneic or isogeneic grafts. The biological effect on stromal cells will be examined by assaying the non-adherent cell population for hemopoietic stem cell self-renewal potential and for numbers of committed (granulocytic, erythroid and megakaryocytic), or uncommitted stem cells.

Our specific objectives are: 1. To develop an in vitro assay for the engraftment of stem cell onto bone marrow stroma, 2. to examine stem cell production after engraftment, 3. to observe the effect of chemotherapeutic agents on bone marrow stromal cells in vitro, 4. to determine the effect of cytotoxic drugs on engraftment, and 5. to evaluate the effect of drug treatment on the development of committed and uncommitted stem cells in the in vitro long-term bone marrow liquid system.

106. REGULATION OF ERYTHROID DIFFERENTIATION IN MURINE AND HUMAN LEUKEMIA AND THE GENETIC CONTROL OF HOST CELL RESPONSE TO LEUKEMOGENIC VIRUS

Axelrad, A. A., McLeod, D. L., Amato, D., Wu, A. M., Croizat, H., St. Rose, J., University of Toronto, Faculty of Medicine, Dept. of Anatomy (Histology), *92 College St., Toronto, Ontario*, M5S 1A8, Canada

We have recently reported that Fv-2 on chromosome 9 of the mouse, the locus originally identified as a major determinant of host susceptibility (Fv-2s) or resistance (Fv-2r) to Friend erythroleukemia virus (FV), also functions in normal animals, where it determines whether a high (Fv-2s) or low (Fv-2r) proportion of erythropoietic progenitor cells (BFU-E) are normally engaged in DNA synthesis. The effect of the Fv-2 gene appears to be specific for BFU-E; it has no effect on DNA synthesis of CFU-S, CFU-E or CFU-Gm (CFU-C). The effect of the gene also seems specific for a point in the cell cycle: most BFU-E of Fv-2rr mice are normally arrested at or near the G1/S boundary, while BFU-E of Fv-2ss mice continually cycle. We wish to answer the question of whether the Fv-2 gene operates within the BFU-E itself or in another cell to determine the production of a factor that controls entry of BFU-E into DNA synthesis.

Preliminary bone marrow transplantation experiments in vivo indicate that the latter alternative is more probable. We are now searching for factors in the bone marrow of B6 (Fv-2rr) and B6.S (Fv-2ss) mice that differ in their influence on the proportion of BFU-E killed by exposure to high specific activity 3H-dThd in vitro.

With the work on murine cells as a guide, studies continue on the role of regulatory factors in the control of proliferation and differentiation of hemopoietic progenitor cells in vitro in the human myeloproliferative disorders.

BIBLIOGRAPHIC REFERENCES: Mak, T.W., Axelrad, A.A. and Bernstein A. Fv-2 locus controls expression of Friend spleen focus-forming virus-specific sequences in normal and infected mice. Proc. Natl. Acad. Sci. USA 76, 5809-5812, 1979. Susuki, S. and Axelrad, A.A. Fv-2 locus controls the proportion of erythropoietic progenitor cells (BFU-E) synthesizing DNA in normal mice. Cell 19, 225-236, 1980.

107. F1 ANTIPARENTAL CELL-MEDIATED LYMPHOLYSIS IN VITRO

Shearer, G. M., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Immunology Branch, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

Mouse F1 spleen cells develop cytotoxic activity in vitro against parental cells. The antigenic differences detected appear to be controlled by a structural gene (Hh-1) mapping in or near the D region of the H-2 complex. Although a number of positive correlations have been demonstrated between murine hemopoietic graft rejection in vivo and F1 anti-parent cytotoxicity in vitro, certain differences have been found between these two F1 anti-parent reactions. These include the observations that marrow graft rejection does not require priming and is not dependent upon thymus-dependent cells, whereas the development of cytotoxic cells requires sensitization and is effected by T-lymphocytes. The same mechanism is also responsible for the rejection of hemopoietic allografts. Injection of F1 mice with parental spleen cells (which have graft vs. host potential) results in the specific abrogation of F1 anti-parent reactions in vitro and in vivo, whereas injection of parental bone marrow is associated with some degree of priming for F1 anti-parent cytotoxicity.

BIBLIOGRAPHIC REFERENCES: Cudkowicz, G., Landy, M., and Shearer, G.M. (Eds.): Natural Resistance to Foreign Hemopoietic and Leukemia Grafts. New York, Academic Press, 1979, 289 pp. Shearer, G., Waksal, H., Yung, Y. P., and Cudkowicz, G.: Depressive effect of silica particles on F1 hybrid anti-parent cell-mediated lympholysis induced in vitro. Cell. Immunol. 39: 61-69, 1978.

108. 6-14C-ARGININE PULSE LABELING OF PLASMA CELL NEOPLASMS

Humphrey, R. L., Johns Hopkins University, School of Medicine, Dept. of Oncology, *725 N. Wolfe St., Baltimore, Maryland*, 21205, United States of America

We have developed a simple, sensitive, specific and reproducible technique for quantitating the newly synthesized tumor secreted M component biomarkers using in vivo radiolabeling with 6-14C-arginine. With this technique, we are able to detect as few as 1 x 10 to the 6th power plasma cells in the mouse and we can repeatedly measure the total body burden of malignant plasma cells in the murine plasmacytoma system (LPC-1 in BALB/c mice) and multiple myeloma in man. Further study of the mouse model is needed in order to identify and understand the interrelationship of tumor cell and host factors and the effect on these factors of various modes of treatment (chemo-, radio- and immunotherapy) that may modify M component synthesis. We also plan to study the mouse plasmacytoma system as a model for autologous bone marrow transplantation with the objective of developing a more aggressive approach to the therapy of this disorder in man. These studies are designed to complement similar studies in man and to permit the development of concepts and techniques which will be applied in the parallel human studies. Body burden measurements in man will be correlated with other parameters of the extent of the disease, the effect of therapy, survival and remission/response duration. A better understanding of the interrelationship between tumor cell and host factors as probed by 6-14C-arginine pulse labeling technique will help in improved assessment of the nature and extent of the disease and in development of new approaches to therapy.

B. LEUKOCYTE TRANSFUSIONS

109. HYPERTRANSFUSION IN ACUTE MYELOID LEUKEMIA

Ekert, H., Toogood, I. R., Waters, K. D., Royal Children's Hospital, Dept. of Clinical Haematology & Oncology, *Flemington Rd., Parkville, Victoria 3052, Australia*

OBJECTIVE: To investigate the effect of hypertransfusion on the proliferative activities of myeloblasts.

PROJECT: Children with AML and a white cell count below 50,000 will be hypertransfused to a Hb. of 16-18 g/dl prior to commencing chemotherapy. Bone marrow aspirations will be performed before, and 96 hours after, hypertransfusion. Bone marrow morphology, cellularity, labelling indices and culture characteristics will be determined.

PROGRESS: Ten patients have so far been investigated. In 6, hypertransfusion has resulted in a significant increase in L.I. to cells which, morphologically and by culture, appear to be myeloblasts. Patients with an increase in L.I. after hypertransfusion have come into remission. Patients without an increase in L.I. after hypertransfusion have not remitted.

110. EASTERN COOPERATIVE ONCOLOGY GROUP

Lerner, H. J., Zaren, H., Pennsylvania Hospital, Section of Surgical Oncology & Cancer Chemotherapy, *8th & Spruce Sts., Philadelphia, Pennsylvania*, 19107, United States of America

The major objectives are the overall objectives of the ECOG. These include: 1) The early evaluation of anti-cancer compounds. 2) The pharmacology, toxicology and efficacy of such compounds. 3) The acquisition of knowledge concerning the biology and patterns of expression of malignant disease.

Of additional particular interest to the principal investigator is: 1) Combination therapy (chemotherapy plus concomitant radiotherapy) in the management of locally advanced cancer. 2) The early chemotherapy of cancer when present but not yet measurable. 3) Large dose multi-drug chemotherapy of advanced cancers. 4) Interdisciplinary approach to care of the cancer patient. 5) Treatment of metastatic breast cancer with anti-estrogens (Tamoxifen) and its correlation to estrogen receptor proteins. 6) The use of WBC transfusions in septic, neutropenic patients. 7) The use of central and peripheral hyperalimentation in patients receiving multi-modal therapy, especially advanced head and neck cancers.

BIBLIOGRAPHIC REFERENCES: Vogl, S., McCormick, B., Coughlin, C., Lerner, H., and Kaplan, B. Chemotherapy with Cis-Platinum, Methotrexate and Bleomycin As Initial Treatment for Regionally Advanced Head and Neck Cancers. Submitted for presentation at the 62nd Annual Meeting of the American Radium Society, Philadelphia, PA, April 1980. Lerner, H., Carbone, P., and Kalbfleisch, J. Intermittent Parenteral Methotrexate (EST 2365). Submitted for presentation at the 16th Annual Meeting of the American Society of Clinical Oncology, San Diego, CA, May, 1980.

111. GRANULOCYTE SUPPORT - CRYOPRESERVATION OF AUTOLOGOUS BONE MARROW

Deubelbeiss, K. A., Odavic, R. O., Beck, E. A., Inselspital, Hematology Laboratory, *CH3010 Bern, Switzerland*

OBJECTIVES: Project A: Characterization of variables influencing the rate of transfused neutrophils. Project B: Cryopreservation of human bone marrow; characterization of optimal storage conditions; clinical evaluation.

APPROACH: Project A: Evaluation of variables influencing leucocyte collection and transfusion using DF32 P-labelling and skin window technique. Project B: Evaluation of optimal storage conditions using the CFUc assay. Clinical assessment of autologous marrow transfusion in patients with CML.

112. AML IN ADULTS - PROPHYLACTIC GRANULOCYTE TRANSFUSIONS - RESULTS OF A RANDOMIZED CONTROLLED TRIAL IN PATIENTS WITH AML (ABBREV)

Ford, J. M., Cullen, M. H., Roberts, M. M., Oliver, R. T., Lister, T. A., Imperial Cancer Research Fund, Medical Oncology Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Between February 1972 and August 1977 we conducted a prospective randomized controlled clinical trial of granulocyte transfusions in an attempt to reduce the morbidity and mortality from infection in adults with newly diagnosed acute myelogenous leukemia (AML). The granulocytes were harvested from normal donors using the Hemonetics Cell Separator Model 30 and the transfused patients received a median dose of 1.45 times 10 to the 10th power cells (range 0.26-3.45 times 10 to the 10th power) on alternate days during the period of marrow aplasia induced by the initial course of antileukemic chemotherapy. The transfusions were given when the patients' own absolute granulocyte levels were less than 0.5 times 10 to the 10th power/liter. Thirteen patients received from 1-12 granulocyte transfusions and 11 patients acted as controls. No significant advantage was demonstrated in the transfused patients with regard to the following parameters: 1. deaths due to infection; 2. reduction in the frequency of pyrexial episodes; 3. delay in the onset of pyrexial episodes; 4. reduction in the length of pyrexial episodes; 5. reduction in the frequency of proven infection.

113. AML IN ADULTS - THE INCIDENCE OF ALLOIMMUNIZATION TO GRANULOCYTES AND PLATELETS FOLLOWING PROPHYLACTIC TRANSFUSIONS (ABBREV)

Ford, J. M., Cullen, M. H., Imperial Cancer Research Fund, Medical Oncology Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Twenty-six acute myelogenous leukaemia (AML) patients received a total of 214 combined transfusions of granulocytes and platelets obtained from normal donors during a trial of prophylaxis against infection. The patients were monitored carefully for the development of transfusion reactions and whenever possible blood samples were taken to calculate the percent recovery in the circulation of granulocytes and platelets at one hour and of platelets at 20 hours. Of the 23 evaluable patients, 12 developed severe transfusion reactions to at least one donor. Transfusion reactions were accompanied by significant reductions in the recoveries of platelets and granulocytes. There was a highly significant reduction in the recoveries of granulocytes and platelets with increasing numbers of transfusions given. The results suggest that granulocyte recoveries of less than five percent at one hour and platelet recoveries of less than 15 percent at one hour or ten percent at 20 hours are indicative of alloimmunization to these cells.

Although five patients were apparently only alloimmunized to platelets, the 12 patients who had transfusion reactions and were alloimmunized to granulocytes also had low platelet recoveries. Only six patients had no transfusion reactions and were apparently alloimmunized to neither cell type. These results indicate an alarming incidence of alloimmunization following granulocyte transfusions.

114. INFECTIONS IN CANCER PATIENTS

McCredie, K. B., Hester, J. P., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Developmental Therapeutics, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas,* 77030, United States of America

In this study, 34 acute leukemia patients undergoing remission induction chemotherapy have received prophylactic granulocyte replacement transfusions in an effort to prevent or reduce the incidence of infection associated with myelosuppressed patients with neutropenia. There was a median treatment period of 8 weeks, range 2-16, to achieve a remission status of CR for 27 (79%), PR for 2 (6%), and fail for 5 (15%) patients. This represents an improvement over a 67% CR and 4% PR rate for 258 patients receiving comparable chemotherapy, but who did not receive prophylactic granulocytes. A reduction was noted in the incidence of pneumonia in patients on the prophylactic study (5.5%), compared to 202 patients not on the study (20%), but the incidence of primary bactermia was not reduced. The severity of infection correlated with the duration of neutropenia and absence of infection could be documented in only 3 patients who had less than 15 days of neutropenia. Myelosuppression is a recipient biologic variable which can be neither predicted nor controlled. The inability to maintain an infection-free status for more patients was felt to relate to: 1) Insufficient numbers of transfusions during neutropenic episodes extending beyond 15 days; 2) inadequate cell doses to provide a physiologically appropriate granulocyte level in the recipient; 3) inadequate numbers of primary family related donors (siblings, parents, offspring) to support recipients during extended periods of neutropenia; 4) emergence of symptomatology in a few donors following multiple leukapheresis which had not been previously seen. All four areas are under investigation so that more effective replacement may be planned for additional patients entering the study.

BIBLIOGRAPHIC REFERENCES: Hester, J.P., Kellogg, R.M., Mulzet, A.P., McCredie, K.B., and Freireich, E.J.: Principles of continuous-flow cell separation in a circumferential flow disposable channel. In: Methods of Cell Separation, Vol. III, Plenum Press (New York), 1980, in press. Hester, J.P., McCredie, K.B., and Freireich, E.J.: The relationship of histocompatibility antigens and ABO typing and post-transfusion granulocyte increments. Transplantation Proceedings, 1980, in press.

115. CANCER CLINICAL RESEARCH CENTER

Henderson, E. S., Preisler, H. D., Higby, D. J., Han, T., Ozer, H., Gomez, G., Roswell Park Memorial Inst., Dept. of Medical Oncology, *666 Elm St., Buffalo, New York,* 14263, United States of America

The Cancer Clinical Research Center's primary goal is to develop optimal regimens for patients with disseminated cancer. At present, research is concentrated on the hematological malignancies: acute and chronic leukemias, Hodgkin's disease, non-Hodgkin's lymphoma, and multiple myeloma. Techniques are being developed for the identification and separation of subsets of malignant and normal hematopoietic tissues, and for analysis of their function, the capacity for self-renewal, their sensitivities to normal stimuli and to drugs and radiation, and their recognition by immunological means. From this information increasingly specific regimens will be developed and tailored for each patient with the intent of curing the malignancy and preventing recurrence of new lesions. Supportive care with transfusions of mature lymphocytes, granulocytes and stem cells, plus evaluation of new antimicrobial agents will provide the margin of safety necessary to provide aggressive chemo-radiotherapeutic regimens. Sophisticated computer assisted data collection and analysis will examine the information to be gained and disseminated from this research.

116. SUPPORTIVE CARE - CLINICAL EVALUATION OF GRANULOCYTE TRANSFUSION (HUMAN)

Higby, D. J., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York,* 14263, United States of America

This is part of a broader project. A summary of this subproject is not available.

117. SEPARATION AND COLLECTION OF LEUKOCYTES

Bottomley, R. H., Hussein, K. K., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology Section, *921 N.E. 13th St., Oklahoma City, Oklahoma,* 73104, United States of America

The objective of this study is to collect granulocytes from normal donors for the purpose of transfusion to patients with seriously compromised bone marrow in order to prevent or eradicate infection and to leukapherese patients with various types of leukemia as a form of therapy and to freeze and store leukemic cells for in vitro experimental studies.

A total of 8 V.A. patients have been registered on this protocol during this year. A total of 41 white blood cell transfusions have been given to the 8 patients. The project is ongoing with no changes in the protocol.

118. SUPPORTIVE TREATMENT WITH GRANULOCYTES AND THROMBOCYTES

Zaroulis, C. G., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

119. FACTORS INFLUENCING THE FUNCTION OF TRANSFUSED GRANULOCYTES

Higby, D. J., Gilani, S. S., Park, B. H., Roswell Park Memorial Inst., Medical Oncology Dept., *666 Elm St., Buffalo, New York,* 14263, United States of America

Preliminary evidence has been developed which demonstrates that serologic factors exist in neutropenic infected leukemic patients which: a) Alter chemotaxis of donor granulocytes; b) reduce phagocytosis of oil droplets incubated in recipient serum; and c) predict, to some extent, outcome (fatal or nonfatal) of anti-infective therapy. The proposed study has as its objective to enlarge upon those observations, to test whether: a) Serologic factors predict clinical events related to the transfusion of granulocytes, and b) in vitro studies reflect in vivo behavior of transfused granulocytes.

Methods will consist of: a) Determining the effects of recipient serum on donor granulocytes in chemotaxis and oil-red-O opsonization assay systems; b) labelling the donor granulocytes with Indium 111 and observing in the recipient: 1. Ability of labelled cells to migrate into skin chambers. 2. Intravascular survival and kinetics of labelled donor cells. 3. Final distribution of label with gamma imaging.

Finally, clinical parameters will be followed and entered into a computer system for later correlative analysis. In addition to standard parameters, forced sorting methods for quantifying clinical observations will be collected and cumulative sum-plotting of the temperature curve will be used.

Logistic regression and Cox modeling approaches will be used to deal with the data generated.

The ability to identify in advance those patients who will do poorly with broad spectrum antibiotic therapy and granulocyte transfusions will permit a concentrated effort to be directed at those factors which are responsible for this in the hopes of improving survival in neutropenic infected patients.

120. IMPORTANCE OF GRANULOCYTE ANTIGENS IN LEUCOCYTE TRANSFUSIONS AND BONE-MARROW TRANSPLANTATIONS

Jeannet, M., Cruchaud, A., vonFliedner, W., Hopital Cantonal, Transplantation Immunology Unit, *64 Ave. de la Roseraie, 1211 Geneva 4, Switzerland*

The summary for this project is under entry no. 70.

121. PROTECTIVE ENVIRONMENT AND GRANULOCYTE TRANSFUSION (HUMAN)

Buckner, C. D., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington,* 98104, United States of America

The summary for this project is under entry no. 31.

122. SEPARATION OF BLOOD BY CONTINUOUS CENTRIFUGE

Thomas, E. D., Buckner, C. D., Clift, R. A., Weiden, P., Fred Hutchinson Cancer Research Center, Dept. of Medicine, *1124 Columbia St., Seattle, Washington,* 98104, United States of America

The summary for this project is under entry no. 30.

C. PLATELET TRANSFUSIONS

123. EXPERIMENTAL AND CLINICAL STUDIES OF HEMOSTASIS DURING SURGERY FOR LIVER DISEASES

Bengmark, S., Goransson, G., Elmer, O., Pihlblad, P., Zoucas, E., Lunds Universitet, Dept. of Surgery, *Lasarettet, S22101 Lund 7, Sweden*

OBJECTIVE: To study hemostasis in individuals with liver diseases and after liver resection in experimental animals and in patients with special regard to the effects of transfusion and infusion treatment.

APPROACH: Standardized liver resection is performed in rats. Bleeding time and blood loss as well as coagulation and platelet function are studied. Rats are pretreated with colloids or pharmacological agents such as salicylic acid or trauma such as femoral fractures. The effect of infusion of bank blood on volume and number of platelet aggregates in circulating blood is studied in patients during surgery.

METHODS: Physiological parameters are studied with thermodilution technique. Hemoglobin, hematocrit, platelet count, fibrinogen, platelet factor III and platelet factor IV are determined. Screen filtration pressure according to Swank is our screening method for finding aggregates. Platelet aggregation is determined according to Born. A new method to study volume and number of microaggregates in circulating blood has been devised by Solis of Houston, Texas. The method involves the use of a Coulter counter for counting the platelet aggregates. Aggregates of different sizes are grouped and their volume recorded via a channellyzer. Microcirculation is studied in collaboration with professor Blumgart of the Royal Infirmary, Glasgow.

PROGRESS: Preliminary studies in the rat performed in 1978 show increased bleeding time and blood loss after pretreatment with dextrans, degraded gelatin and hydroxyethyl starch. Salicylates increase bleeding time and blood loss whereas bilateral femoral fractures one hour before liver resection give a reduced bleeding time and blood loss.

Preliminary experiments in patients have shown an increased screen filtration pressure and decreased platelet count one hour after infusion of degraded gelatin.

During 1979 and thereafter we plan to study hemostasis and microaggregate formation during liver surgery in patients, as well as the effects of anaesthesia, infusion of salt solutions, carbohydrate solutions and colloids as well as transfusion with whole blood and packed red blood cells with and without microfiltration.

124. CELL TRANSFUSION THERAPY

Schiffer, C. A., Aisner, J., Wiernik, P. H., Terasaki, P., Kotelba Witkoska, B., Dutcher, J. P., Johnson, G., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Oncology Branch, *Baltimore, Maryland,* 21201, United States of America

Management of alloimmunized patients has been facilitated by further expansion of the HLA matched donor pool and continued growth of the autologous frozen platelet transfusion program. Studies of patients with non-lymphocytic leukemia have demostrated that the development of alloimmunization is not related to the number of platelet transfusions received. With few exceptions, patients who did not develop lymphocytotoxic antibody within 6-8 weeks of platelet transfusion never developed antibody despite subsequent transfusions, possibly suggesting a state of immune tolerance to histocompatibility antigens. A randomized study comparing the rate of alloimmunization in patients receiving lymphocyte depleted and 'standard' platelet concentrations is in progress. Platelet cryopreservation using glycerol-glucose as the cryoprotective agents has demonstrated good freeze-thaw recovery but significant loss of ATP and morphologic integrity. Indium labeled granulocytes migrate to infected sites within 30 minutes of transfusion and have been shown to be a relatively simple and reliable label permitting excellent scanning and kinetic analysis. Studies are in progress using this technique to determine the effect of alloimmunization on granulocyte migration after transfusion.

BIBLIOGRAPHIC REFERENCES: Schiffer, C.A., Alisner, J.: Rational approach to granulocyte transfusion therapy. In Contemporary Hematology/Oncology, LoBue, J., Gordon, A.S., Silber, R., Plenum Publishing Corp, N.Y. pp. 201-218, 1980. Love, L.J., Schimpff, S.C., Schiffer, C.A., Wiernik, P.H.: Improved prognosis for granulocytopenic patients with gram-negative bacteremia. Amer. J. Med. 68: 643-648, 1980.

125. PLATELET TRANSFUSION AND COAGULATION (HUMAN)

Slichter, S. J., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington,* 98104, United States of America

This is part of a broader project. A summary of this subproject is not available.

126. HLA TYPING FOR PLATELET AND LEUKOCYTE TRANSFUSIONS

Terasaki, P. I., University of California, Los Angeles Campus, School of Medicine, Dept. of Surgery, *2025 Zonal Ave., Los Angeles, California,* 90024, United States of America

OBJECTIVE: Provide tests needed for efficacy of HL-A phenotyping for the identification of compatible donors in cancer patients. The test protocol is designed to establish if HL-A matched platelet support provides any real advantage over single donor unmatched platelet support in cancer patients. It also provides the opportunity to test the utility of two other in vitro assays of donor recipient compatibility, lymphocytotoxicity, and platelet migration inhibition assays.

127. PLATELETPHERESIS SERVICE - DIVISION OF CANCER TREATMENT

Welcome, G. R., Community Blood & Plasma Services, *1633 E. Lombard St., Baltimore, Maryland,* 21231, United States of America

OBJECTIVE: Provide plateletpheresis services for the Clinical Center and Clinical Oncology Program, DCT, NCI, for platelet transfusions to protect thrombocytopenic cancer patients.

128. AML IN ADULTS - THE INCIDENCE OF ALLOIMMUNIZATION TO GRANULOCYTES AND PLATELETS FOLLOWING PROPHYLACTIC TRANSFUSIONS (ABBREV)

Ford, J. M., Cullen, M. H., Imperial Cancer Research Fund, Medical Oncology Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

The summary for this project is under entry no. 113.

129. RANDOMIZED STUDY OF HYPERTRANSFUSION IN CHILDHOOD ACUTE LYMPHOCYTIC LEUKEMIA

Ekert, H., Smith, P. J., Toogood, I., Royal Children's Hospital, Clinical Haematology & Oncology, *Flemington Rd., Parkville, Victoria 3052, Australia*

OBJECTIVES: To determine whether moderate hypertransfusion (Hemoglobin 14-18gm%) can reduce duration of neutropenia and severity of infections in ALL and to study the mechanisms of this protective effect.

APPROACH: Paired randomization has been adopted. All children receive identical chemotherapy. Blood investigations are performed 2 times a week; bone marrow culture in soft agar performed on Day 14; erythropoietin levels to be assayed in both groups of patients.

PROGRESS: Preliminary findings (Lancet I, 776, 1976) show that there was a significantly greater polymorphonuclear count on Day 10 in hypertransfusion group; significantly diminished incidence of infections; and significant reduction in interruptions to chemotherapy. Randomization of 12 pairs of children with ALL confirms these findings. Bone marrow culture has not yet been performed in sufficient numbers of patients to permit evaluation.

Randomized study (Lancet) shows significantly greater polymorphonuclear counts on Days 7 and 10 in hypertransfused group; reduction in incidence of infection and interruptions to chemotherapy. Bone marrow studies suggest that 'stem cell competition' may be the mechanism of action.

130. BLOOD PRODUCTS AND SUPPORTIVE CARE (HUMAN, RATS)

Yankee, R. A., Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts,* 02115, United States of America

This is part of a broader project. A summary of this subproject is not available.

131. AUTOLOGOUS MARROW AND PERIPHERAL BLOOD HEMATOPOIETIC STEM CELLS IN ACUTE LEUKEMIA - HARVESTING, CRYOPRESERVATION, REINFUSION

Rybka, W. B., Montreal General Hospital, Research Institute, *1650 Cedar Ave., Montreal, Quebec,* H3G 1A4, Canada

OBJECTIVE: To determine if autologous cryopreserved peripheral blood hematopoietic stem cells have any advantage over marrow cells in the therapy of acute leukemia.

APPROACH: In adult patients with either acute lymphoblastic leukemia or acute non-lymphoblastic leukemia, harvesting of hematopoietic stem cells from the marrow and peripheral blood will be undertaken. The quantity of circulating granulocyte precursors (CFUc) as a function of time following certain courses of chemotherapy will be determined. A comparison of growth characteristics in culture of leukemic blasts and normal remission cells will be undertaken. After determining the optimum time for harvesting remission hematopoietic stem cells, both marrow and peripheral blood cells will be harvested. These cells will be subsequently frozen and stored. The conditions of cryopreservation and storage will be closely observed. When the patients, so studied, relapse on conventional chemotherapy, they will be offered treatment with high dose cyclophosphamide and total body irradiation, a regimen known to eradicate leukemic cells, in the hope of providing a prolonged remission. Marrow repopulation will be attempted with cryopreserved autologous cells. The repopulation ability of peripheral blood cells will be assessed.

132. THE STUDY OF INTENSIVE CHEMOTHERAPY AS AN ADJUNCT TO SURGERY AND RADIOTHERAPY FOR MALIGNANT GLIOMAS

Weiner, R. S., Day, A., Noyes, W. D., Kitchens, C. S., Ross, W., Streiff, R. R., Kramer, B., Gefter, J., Ballinger, W., Thar, T. L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *Gainesville, Florida,* 32601, United States of America

The design of this study is to determine the therapeutic effectiveness of nitrosourea when dose and schedule can be maintained.

The objectives are: To determine whether the infusion of autologous stem cells following nitrosourea chemotherapy can reduce the degree and duration of myelosuppression, and to determine the hematologic and immunologic responses in patients receiving nitrosureas with and without autologous stem cell reinfusion.

133. SUPPORTIVE CARE - AUTOLOGOUS STEM CELL SUPPORT

Yankee, R. A., Sidney Farber Cancer Center Inc., *44 Binney St., Boston, Massachusetts,* 02115, United States of America

This is part of a broader project. A summary of this subproject is not available.

D. TECHNIQUES FOR PREPARATION AND PRESERVATION OF BLOOD COMPONENTS

134. LEUKAPHERESIS LABORATORY (HUMAN)

Perez Santiago, E., University of Puerto Rico, Medical Sciences Campus, School of Medicine, Dept. of Medicine, *P.O. Box 5067, Rio Piedras,* 00936, Puerto Rico

This is part of a broader project. A summary of this subproject is not available.

135. SUPPORTIVE CARE - IMPROVING GRANULOCYTE COLLECTION TECHNIQUES (HUMAN)

Higby, D. J., Roswell Park Memorial Inst., *666 Elm St., Buffalo, New York,* 14263, United States of America

This is part of a broader project. A summary of this subproject is not available.

III. NUTRITIONAL EVALUATION AND SUPPORT OF CANCER PATIENTS

A. ASSESSMENT OF NUTRITIONAL STATUS

1. METHODS OF DETERMINING NUTRITIONAL CONDITION

136. INVESTIGATION OF THE RELATIONSHIP BETWEEN CELL-MEDIATED IMMUNITY AND NUTRITIONAL STATUS IN HUMANS WITH CANCER

Burke, M., Kark, A. E., Clinical Research Centre, Oncology Unit, *Watford Rd., Harrow, Middlesex, United Kingdom*

OBJECTIVE: To investigate the part played by malnutrition in cancer patients in altering metabolic and immune responses.

APPROACH: Measurements of anthropomorphic parameters, total body potassium, total body water, erythrocyte potassium and water, resting metabolic rates, dietary intake, and in vitro and in vivo lymphocyte function were performed on 27 patients with benign disease and 48 with malignant gastrointestinal disease. The results have been analyzed under the headings of: (a) Changes in body composition in mild/moderate undernutrition in benign and malignant gastrointestinal disease. (b) Dietary intake and energy expenditure in the aetiology of weight loss in benign and malignant gastrointestinal disease. (c) Undernutrition and cell-mediated immunity in gastrointestinal cancer. Additional studies on the prediction of fat free mass by multiple parameters in undernutrition, changes in erythrocyte composition in gastrointestinal disease, and the assessment of the Oxylog machine for clinical practice have been completed.

PROGRESS: a. A decrease in the ratio of total body potassium:total body water is a sensitive indicator of early undernutrition which is independent of degree or duration of weight loss or the nature of the underlying disease. b. Changes in the erythrocyte composition confirm that the above ratio probably reflects shifts in intracellular and extracellular water while intracellular potassium concentration is stable. c. The ae-

tiology of undernutrition is similar in benign and malignant disease, and weight loss can be attributed to a decrease in total energy intake indicating the therapeutic need for nutrition repletion in cancer patients.

137. NUTRITIONAL ASSESSMENT OF THE CANCER PATIENT

Bozzetti, F., Baticci, F., Bonalumi, M. G., Scott, A., Istituto Nazionale per lo Studio e la Cura dei Tumori, *1 Via G Venezian, 20133 Milan, Italy*

OBJECTIVE: The purpose of this prospective study is the evaluation of the nutritional status of the cancer patient with relation to (a) type of tumor, (b) the stage of disease, and (c) the therapy performed.

APPROACH: Evaluation parameters include: change of weight, triceps skinfold, arm circumference, flexed biceps arm circumferance, upper arm muscle circumference, creatinine/height index, serum albumin and transferrin, cholinesterase, total peripheral lymphocyte count per cubic mm, fraction c3-c4 of complement, skin tests.

PROGRESS: The study is in progress. Two hundred fifty patients will be evaluated.

138. NON-SPECIFIC IMMUNITY IN PATIENTS WITH SOLID TUMORS

Campani, M., Dionigi, R., Zonta, A., Dominioni, L., Universita degli Studi di Pavia, Istituto di Patologia Chirurgica, *27100 Pavia, Italy*

Evaluation of non-specific immunoreactivity has been performed in 222 cancer patients. Preliminary conclusions can be drawn concerning the following topics: 1) Correlations between immunocompetence and incidence of postoperative infections; 2) nutritional status; 3) immunological aspects of surgical trauma; 4) natural history of the tumor and postoperative course.

Immunocompetence and postoperative infections: Delayed hypersensitivity response (DHR) in this patient population shows that 41% are normoergic, 50% hypoergic and 9% anergic. One or more postoperative infectious episodes developed in 36% of normoergic patients, 49% of hypoergic patients, and 86% of anergic patients. Patients who are preoperatively anergic to skin tests present a higher risk of postoperative infections regardless of the degree of intraoperative contamination.

Immunocompetence and nutritional status: Multiple anthropometric measurements and biochemical indicators of nutritional status have been assayed. Parameters which were significantly altered in neoplastic patients are: percentage of usual body weight and percentage of arm muscle circumference, Hb, albumin, iron, retinol binding protein. Ceruloplasmin was significantly increased and correlated with postoperative infections.

Immunological aspects of surgical trauma: Correlation between postoperative immunodepression and duration of anesthesia, blood transfusions, steroid administrations and surgical trauma on tissues have been assayed in neoplastic patients undergoing radical surgery. Postoperative depression of cellular immunity assayed by means of lymphocyte blastogenic response to PHA correlated significantly with the amount of surgical trauma, whereas it did not correlate with the volume of blood transfusions, nor with the steroid administrations, nor with the duration of anesthesia.

Natural history of the tumor and postoperative course: In this study preoperative determinations of total lymphocyte counts, T-cells in peripheral blood and lymphocyte blastogenic response to PHA are slightly depressed in cancer patients compared to age-matched normal controls. No prognostic clinical value could be attributed to these parameters of the clinical course during the first 6 post-operative months. Anergy to skin tests represents an unfavorable prognostic index. Preliminary results of humoral immunity and neutrophil function tests did not show major derangements of normal values.

139. NUTRITIONAL STATUS OF CANCER PATIENTS

Sisson, G., Northwestern University, Chicago Campus, School of Medicine, Dept. of Medicine, *303 E. Chicago Ave., Chicago, Illinois,* 60611, United States of America

This is part of a broader project. A summary of this subproject is not available.

140. EFFECTS OF CHEMOTHERAPY ON NUTRITIONAL STATUS

Laszlo, J., Duke University, School of Medicine, Dept. of Medicine, *Box 3711, Durham, North Carolina,* 27710, United States of America

This is part of a broader project. A summary of this subproject is not available.

141. ASSESSMENT OF THE NUTRITIONAL STATUS OF CANCER PATIENTS

Bozzetti, F., Istituto Nazionale per lo Studio e la Cura dei Tumori, *1 Via G Venezian, 20133 Milan, Italy*

Purpose of this study is the evaluation of the nutritional status of the cancer patients in relation to the histological type, the stage and the therapy performed. This investigation will cover about 380 patients admitted to the Istituto Tumori.

Parameters of evaluation include: Weight change (referred to the ideal weight and to the pre-disease weight); skinfold thickness of triceps, biceps, subscapular and suprailiac; Mid-upper arm circumference, mid-upper arm muscle circumference, flexed biceps circumference; serum albumin, transferrin, cholinesterase; creatinine/height index and urinary urea total lymphocyte count; complement (C3-C4); skin tests (PPD, varidase).

142. NUTRITIONAL PARAMETERS IN CANCER PATIENTS

Grant, J. P., Duke University, School of Medicine, Dept. of Surgery, *Box 3711, Durham, North Carolina,* 27710, United States of America

OBJECTIVE: Determine critical nutritional assessment parameters in patients with malignant diseases which can be related to the degree of malnutrition as well as impaired organ function and, subsequently, to increased morbidity and mortality. Secondly, once these critical nutritional assessment parameters have been defined, it will be the objective of this study to monitor changes in these parameters and, specifically, improvement in organ function with the institution of intensive nutritional support.

143. ULTRASONIC ASSESSMENT OF NUTRITIONAL STATUS

Van Eys, J., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas,* 77030, United States of America

OBJECTIVE: Evaluate and validate immunological techniques for assessing the nutritional status of children with and without cancer in both the field and clinical settings. This project will be coordinated with other DNCP projects in the area.

144. ULTRASONIC ASSESSMENT OF NUTRITIONAL STATUS

Haas, J. D., Cornell University, Ithaca Campus, School of Arts & Sciences, Dept. of Nutritional Sciences, *Ithaca, New York,* 14850, United States of America

This project includes the development, testing, and validation of procedures for the ultrasonic measurement in humans and the development of protocols for clinical investigations.

145. BIOSTEREOMETRIC ASSESSMENT OF NUTRITIONAL STATUS

Herron, R. E., Texas Inst. for Rehabilitation & Research, *1333 Moursund Ave., Box 20095, Houston, Texas,* 77025, United States of America

OBJECTIVES: Determine, using biostereometrics, the body surface area, volume, and density of adult and pediatric normals and cancer patients with and without nutritional support before, during, and after treatment for their disease. Determine the clinical and nutritional status of these individuals at the same point in time. Correlate biostereometric data with clinical and nutritional data.

146. NUTRITIONAL ASSESSMENT AND MONITORING OF NORMAL AND ADULT CANCER PATIENTS

Grant, J., Duke University, School of Medicine, Dept. of Surgery, *Box 3711, Durham, North Carolina,* 27710, United States of America

This is part of a broader project. A summary of this subproject is not available.

147. EFFICACY OF CALORIC SUBSTANCES AND CHANGES IN BODY COMPOSITION IN PARENTERAL NUTRITIONAL SUPPORT

Mullen, J. L., Steinberg, J. J., University of Pennsylvania, School of Medicine, Dept. of Surgery, *36th & Hamilton Walk, Philadelphia, Pennsylvania*, 19174, United States of America

The specific objectives of this program are to define the alterations in body composition which occur in the presence of three major disease entities. These entities are commonly encountered clinically, and probably represent the three major etiologies of nutritional compromise in the hospitalized patient: inadequate diet, stress, and the presence of tumor. These occur in varying combinations clinically and in this program will be evaluated in all possible combinations. A further objective of this program is to evaluate the efficacy of nutritional support in minimizing or correcting any alterations in body composition which are present. Different nutritional regimens will be evaluated in an effort to define the most efficacious in a particular clinical situation. Study animals will be provided with caloric and protein intakes as defined by RDA requirements. However, these will be supplied in varying proportions to determine the most efficacious ratio of fat to carbohydrate calories.

Finally, by performing a standard nutritional assessment panel concurrent with body composition analysis the relative value of common clinical parameters of nutritional status in reflecting alterations in body composition will be assessed. It is anticipated that eight study groups will be required to cover all possible combinations of stress, starvation, and tumor. For each study group, five diets will be used. For statistical analysis, ten subjects will be required on each diet. Thus, 400 subjects in all will be required for completion of the study. It is anticipated that 20 animals may be completed per month. Thus, the entire time frame for this study is approximately 2 years. The ultimate objective will be to have a retrievable fund of data relating body composition, nutritional support, and underlying disease process which would be applicable to a variety of specific clinical situations. The study will be organized in such a way that each variable (stress, starvation, tumor) will be initially studied individually so that by the end of the first year, the effect of these entities will be defined. In subsequent months the effect of the simultaneous presence of two or even three of these entities will be evaluated.

148. FAT LOSS/WEIGHT LOSS IN PATIENTS WITH CANCER

Axelrod, L., Massachusetts General Hospital, *32 Fruit St., Boston, Massachusetts*, 02114, United States of America

OBJECTIVE: Evaluate and validate the use of common metabolic techniques for the study of lipolysis, such as analysis of plasma free fatty acids, glycerol, ketones, and hormones in evaluating the nutritional status of cancer patients.

2. NUTRITIONAL REQUIREMENTS AND PROBLEMS, INCLUDING MALNUTRITION

149. STUDIES OF DIFFERENTIAL NUTRITIONAL REQUIREMENTS BY HOST

Robertson, J. T., University of Tennessee, Center for the Health Sciences, School of Medicine, Dept. of Neurosurgery, *62 S. Dunlap St., Memphis, Tennessee*, 38103, United States of America

OBJECTIVE: Perform research on cancer patients with malignant brain tumors for the clinical segment of this project. During and after the experimental period, patients will be followed and evaluated to assess their response to direct nutritional therapy. In vivo studies using animal models and in vitro studies will be coordinated with the clinical segment. Experimental protocols and data collection for this project will be coordinated with another similar project to be sponsored by the DNCP. The principal investigator will be expected to preserve and/or make available biological samples and specimens for possible collaborative study by other scientists.

150. NUTRITIONAL REQUIREMENTS IN TREATMENT OF BRAIN TUMORS

Banks, W. L., Virginia Commonwealth University, Medical College of Virginia, Dept. of Surgery, *1200 E. Broad St., Richmond, Virginia*, 23298, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

151. NUTRITIONAL PROBLEMS IN CANCER PATIENTS

Ghavimi, F., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

152. MALNUTRITION IN HOSPITALIZED PATIENTS

Butterworth, C. E., University of Alabama in Birmingham, School of Community & Allied Health, Dept. of Nutrition Sciences, *Tidwell Hall BOO6, University Station, Birmingham, Alabama*, 35294, United States of America

This is part of a broader project. A summary of this subproject is not available.

153. SECRETORY IMMUNE RESPONSE IN MALNOURISHED MOTHERS (ADULTS, CHILDREN)

Laven, G. T., University of Alabama in Birmingham, School of Community & Allied Health, Dept. of Nutrition Sciences, *Tidwell Hall BOO6, University Station, Birmingham, Alabama*, 35294, United States of America

This is part of a broader project. A summary of this subproject is not available.

154. NUTRITION AND IMMUNITY

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This is part of a broader project. A summary of this subproject is not available.

155. REDUCTION OF INFECTION RISK IN DRUG TREATED, MALNOURISHED CANCER PATIENTS

Brubaker, L. H., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *Wrightsboro Rd., Augusta, Georgia*, 30904, United States of America

To discover the role of occult bone marrow damage and neutrophil functional abnormalities contributing to infection risk in malnourished cancer patients, we will study neutrophil function (measuring respiratory burst following phagocytosis of opsonized bacteria), serum complement component levels, and degree of protein-calorie malnutrition in a group of about 200 cancer patients over three years. Twenty malnourished patients will undergo two weeks of appropriate nutritional repletion and tests will then be repeated. The purpose is to determine if any combination of studied factors can predict whether patients will develop unusually severe marrow toxicity and/or bacterial infections. Most (refractory lung cancer) patients will receive treatment with adriamycin and cisdiamminedichloroplatinum, 60 mg/m2 each, every three weeks. Others will receive similar treatment as appropriate for their tumor. All will be studied before the first drug dose and followed for analyzable toxicity for three or more weeks until the next dose is given. Results for each patient will be tabulated and analyzed for factors which predict the occurrence of bone marrow toxicity and/or infection. The results may suggest means of preventing unusually severe toxicity in future patients: for example, hyperalimentation or dose reductions, as appropriate, of the myelotoxic drugs for selected patients. Our results to date indicate that poor neutrophil marrow reserves and defective opsonic capacity of patients' serum are common problems in malnourished cancer patients. The latter returned to normal with two weeks of dietary supplementation in all four patients so treated.

156. OLFACTORY CHANGES AFFECTING FOOD PREFERENCES AND FOOD CONSUMPTION IN CANCER PATIENTS

Vickers, Z. M., Theologides, A., University of Minnesota, St. Paul Campus, Agricultural Experiment Station, Dept. of Nutrition & Food Science, *St. Paul, Minnesota*, 55101, United States of America

OBJECTIVES: Determine effects of progression of cancer and of therapies on olfaction. Identify food odors found to be differentially unpleasant to cancer patients. Identify classes of compounds and single compounds in odors responsible for the differential unpleasantness. Determine processing methods or

preparation methods that prevent or minimize the formation of the above compounds. Develop and test hypotheses to explain relationships between odor perception, anorexia, and cancer.

APPROACH: Patients admitted to the Masonic Cancer Memorial Hospital will be studied. Odors to be tested will be prepared by steam distillation. The distillate will be further fractionated into basic, neutral, and acidic parts before separation by gas chromatography. Fractions would be trapped for later odor assessment. Specific compounds would be identified by mass spectroscopy. Subjects will sniff the odor samples and score them for pleasantness, unpleasantness, and possibly other characteristics. Subjects will also indicate their food habits, likes and dislikes.

PROGRESS: A set of food odors was developed for the purpose of testing cancer patients for aversions to food odors. Approximately 140 patients and 100 controls have scored these odors for pleasantness and intensity. In addition these subjects have completed a questionnaire on food likes and dislikes. Data will be analyzed to determine if cancer patients find some of the food odors different in pleasantness and/or intensity than do healthy controls, and if there is a difference between controls and cancer patients in the relationship between the pleasantness scores for the food odors and the subject's like or dislike score for that food. In addition an experiment was conducted to determine if the pleasantness and/or intensity scores for an odor change when the odor is judged in sample sets with varying degrees of overall pleasantness. Results show that if the same judges score all sample sets, the pleasantness and intensity for an odor change little. When different groups of judges score each set, pleasantness and intensity scores for a constant odor show significant differences between sets.

157. GUSTATORY (TASTE) EVALUATION OF CANCER PATIENTS

Settle, R. G., Kare, M., Mullen, J., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *38th & Woodland Aves., Philadelphia, Pennsylvania,* 19104, United States of America

An evaluation of taste preference and taste recognition thresholds for the four primary taste qualities (sweet, sour, salty and bitter) has been conducted on approximately 147 cancer patients and 69 control patients. Taste preference data was obtained using a nine-point category scaling procedure. Taste recognition thresholds were obtained using a four-alternative forced-choice staircase procedure. Initial analyses indicate there may be an increased bitter recognition threshold for cancer patients with indications of extensive disease processes (e.g., regional nodes, distal nodes, metatases). To date preliminary analyses of the taste preference data have not yielded significant differences between control patients and cancer patient groups based on primary tumor site, histological diagnosis, or tumor stage. Twenty-three cancer patients and 26 control patients have completed a modified form of the U.S. Army Natick Laboratories Food Preference Survey, which was approved by the R and D Committee, Philadelphia VAH, for inclusion in this project after the submission of the initial Medical Research Information System Project Data Sheet for this project. In addition, approximately 28 cancer patients and 23 control patients have rated their preference for food items served to them for lunch and dinner by the dietetic service of the hospital. Analyses of these data are currently under way. The National Cancer Institute has requested that we obtain retrospective data on weight loss in these patients and has extended the contract, under which these studies are being carried out, to April 15, 1979, with a possible further extension to September 15, 1979.

3. CACHEXIA

158. TOTAL METABOLISM OF CANCER CACHEXIA

Morrison, S. D., Radcliffe, J. D., Popp, M. B., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Energy Metabolism Section, *900C Rockville Pike, Bethesda, Maryland,* 20205, United States of America

This project is directed towards identifying the causes of the nutritional depletion and general deterioration of the host, a condition known as cancer cachexia, with a view to blocking or reversing these systemic effects of cancer so that the cancer patient could become more accessible to anti-cancer therapies. The approach involves investigation of total energy, water and other material exchanges, and of the physiological and behavioral control of food and water intake in normal and cancerous organisms.

BIBLIOGRAPHIC REFERENCES: Morrison, S.D. Anorexia and the cancer patient. In Van Eys, Nichols and Seelig (Eds.). Nutrition and Cancer. New York, Spectrum, 1979, pp. 31-47.

159. DEVELOPMENT OF CANCER CACHEXIA HYPOPHAGIS

Ahrens, R. A., University of Maryland, College Park Campus, School of Human Ecology, Dept. of Foods, Nutrition & Institution Administration, *College Park, Maryland,* 20742, United States of America

The project is to investigate the separate and interactive effects of quantitatively imposed exercise and variation in dietary carbohydrate source on the systemic response of rats to growth of tumors, with particular reference to food intake, carcass depletion (cachexia), and blood lactate.

160. SURGERY AND ADJUVANT CANCER THERAPY

Stein, T. P., Mullen, J. L., Buzby, G. P., University of Pennsylvania, School of Medicine, Dept. of Surgery, *36th & Hamilton Walk, Philadelphia, Pennsylvania,* 19174, United States of America

The purpose of this proposal is to investigate the interrelationships between nutrition, tumor growth and cancer related cachexia. A totally parenterally nourished rat tumor model will be used. We are specifically interested in determining (1) whether the cancer related cachexia is amino acid dependent and (2) how the tumor growth rate in vivo depends on the source of calories given to the animal.

4. ANOREXIA

161. EVALUATION OF AGENTS FOR TREATING ANOREXIA IN CANCER

Garattini, S., Istituto di Ricerche Farmacologiche Mario Negri, *Via Eritrea 62, 20157 Milan, Italy*

The feasibility of developing pharmacologic agents to counteract the anorexia and cachexia of cancer in animal models will be explored. The exploration will be developed in three main stages: Review of the literature on anorexia and cachexia associated with cancers and cancer treatments; development and testing of two or more animal models of the anorexia and cachexia that occur in humans with cancer; use of the models to test potential therapeutic agents for positive effects on food intake and nutritional status.

162. ANOREXIA IN ADULT AND PEDIATRIC CANCER PATIENTS

Dutcher, J. N., Children's Hospital at Stanford, *520 Willow Rd., Palo Alto, California,* 94304, United States of America

OBJECTIVE: Collect detailed dietary, nutritional, anthropometric, psychological, metabolic, and physiological data on a wide variety of adult and pediatric cancer patients and suitable control patients. This project, which will be a multi-institutional cooperative effort, deals with the causes and effects of anorexia in adult and pediatric cancer patients. Research will be conducted to allow the formulation of hypotheses on the causes of anorexia and the interrelationship between anorexia, cancer type, treatment modality, and associated phenomena.

163. ANOREXIA IN ADULT AND PEDIATRIC CANCER PATIENTS

Henkin, R. I., Georgetown University, School of Medicine, Dept. of Medicine, *3800 Reservoir Rd. N.W., Washington, District of Columbia,* 20007, United States of America

OBJECTIVE: Collect detailed dietary, nutritional, anthropometric, psychological, metabolic, and physiological data on a wide variety of adult and pediatric cancer patients and suitable control patients. This project, which will be a multi-institutional cooperative effort, deals with the causes and effects of anorexia in adult and pediatric cancer patients. Research will be conducted to allow the formulation of hypotheses on the causes of anorexia and the interrelationship between anorexia, cancer type, treatment modality, and associated phenomena.

164. A CENTRAL MECHANISM FOR ANOREXIA IN CANCER

Fischer, J. E., Chance, W., University of Cincinnati, School of Medicine, Dept. of Surgery, *Eden & Bethesda Aves., Cincinnati, Ohio*, 45221, United States of America

Anorexia contributes, to a large extent, to the cachectic state which is a significant problem in patients with cancer. Many hypotheses have been advanced to explain the inappropriately low food intake in these patients, but they have not been very conclusive. Previous work from this laboratory has suggested that derangements in central nervous system neurotransmitter metabolism, specifically involving indoleamine metabolites, may be involved in the etiology of the anorexia in cancer. These in turn appear to be secondary to disturbances in peripheral metabolism, particularly involving increased lipolysis, perhaps secondary to hyperglucagonemia, resulting in increased plasma free tryptophan, which makes tryptophan more easily available for transport across the blood brain barrier and leads to increased brain serotonin.

The experiments to be carried out in this project involve verifying that in fact such derangements in central serotonin metabolism exist. Further experiments are directed at attempting to abolish or at least delay the onset of cancer anorexia by pharmacological means indcluding serotonin antagonists, or changing the peripheral metabolism and/or preventing penetration of tryptophan through the blood brain barrier. In preliminary studies in patients an attempt is made to verify the presence of such a mechanism in patients.

BIBLIOGRAPHIC REFERENCES: Krause, R., James, J.H., Humphrey, C., and Fischer, J.E.: Plasma and Brain Amino Amino Acids in Walker 256 Carcinosarcoma-bearing Rats. Cancer Research 39:3065-3069, 1979. Krause, R., Humphrey, C., VonMeyenfeldt, M., James, H., and Fischer, J.E.: A Central Mechanism for Anorexia in Cancer - A Hypothesis. Cancer Treatment Reports, (in press) 1980.

165. ANOREXIA AND WEIGHT LOSS IN LUNG CANCER

Costa, G., State University of New York, Health Science Center at Buffalo, School of Medicine, Dept. of Medicine, *3435 Main St., Buffalo, New York*, 14214, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

166. ENDORPHINS AND ANOREXIA OF TUMOR BEARING RATS

Yim, G. K., Lamb, D. R., Purdue University, School of Pharmacy & Pharmacal Sciences, Dept. of Pharmacology & Toxicology, *Life Sciences Bldg., West Lafayette, Indiana*, 47907, United States of America

A number of findings, including the block by the opiate antagonist, naloxone, of selected feeding behaviors (Lowy, Maickel and Yim, 1980) suggest that endogenous opiates (endorphins) are critically involved in the control of normal and pathological food intake. Our preliminary studies revealed identical profiles of feeding deficits in naloxone-treated rats and in Walker 256 tumor bearing SD rats (Walker 256 SD, one of the best studied animal models of cancer cachexia). The initial arm of this project is to confirm and extend these comparisons. Pharmacological and biochemical approaches will then be used to distinguish between possible elaboration by the Walker 256 SD of an opiate or possible suppression of endorphin synthesis, due to elevated corticosteroid levels that are found in the Walker 256 SD. Thus, the overall goals are to determine if the Walker 256 SD has a defective endorphin system; to identify the nature of the defect; and to overcome the anorexia of the Walker 256 SD by bypassing or reversing the endorphin defect. The results obtained should have clinical relevance (especially when in attempts to control the anorexia and cachexia in patients with tumors similar to the Walker 256, eg. the ectopic ACTH producing tumors).

167. TASTE AVERSION AS A FACTOR IN CANCER THERAPY

Smith, J. C., Hofer, K. G., Bilek, F. S., State University System of Florida, Florida State University, School of Arts & Sciences, Dept. of Psychology, *205 Wildwood Dr., Tallahassee, Florida*, 32306, United States of America

Radiation-induced taste aversion in laboratory animals may serve as a model for taste aversions and subsequent anorexia observed in clinical radiation therapy patients. Since the typical radiation procedure used in animal studies differs in a number of important aspects from the exposure conditions employed in clinical situations, it is proposed to study the establishment of radiation induced taste aversion in rats under treatment conditions which mimic clinical procedures. This will involve taste aversion studies with multiple, low-dose, partial-body radiation exposures instead of the usual single, high-dose, whole-body irradiation procedures employed in animal studies. Once the effects of these treatment parameters are established, techniques for blocking radiation-induced taste aversions in rats will be investigated. Specifically, the effects of different doses of antihistamines as well as food deprivation before and after irradiation will be studied to determine the optimal treatment regimen for blocking taste aversions. It is hoped that these studies will suggest prophylactic measures which can be used in clinical radiation therapy. Since treatments such as antihistamine injections could compromise the clinical effectiveness of the radiation in destroying cancer cells, studies will be conducted to test for these effects. In addition, extensive but not invasive data collection will be initiated with human radiation therapy patients. Based on information obtained from hospital records, questionnaires, daily interviews and diaries we will evaluate the incidence of dietary problems, in particular changes in dietary habits, experienced by radiation therapy patients. The initial goal will be to determine whether some of the dietary problems encountered in clinical radiation therapy are the result of radiation-induced taste aversion.

168. LEARNED FOOD AVERSION - A COMPONENT OF CANCER ANOREXIA

Bernstein, I. L., Bernstein, I. D., University of Washington, School of Arts & Sciences, Dept. of Psychology, *Seattle, Washington*, 98105, United States of America

The objective of this project is to evaluate the contribution of learned food aversions to the appetite and weight loss induced by tumors and anti-tumor therapy. The proposed studies are based on our recent demonstrations (a) that learned aversions to specific foods can occur in cancer patients receiving GI toxic chemotherapy; and (b) that in animals, tumor growth alone, in the absence of any aversive therapy, can produce aversions to the available diet.

Using an experimental animal model we intend to (a) define the conditions under which aversions to foods are acquired as a consequence of tumor growth and/or chemotherapy; (b) evaluate whether learned food aversions contribute to anorexia; and (c) evaluate intervention approaches for minimizing or eliminating these learned food aversions.

In the clinic we intend (a) to continue to define the conditions under which learned food aversions are acquired as a consequence of GI toxic chemotherapy as well as to evaluate their impact on the nutritional status of cancer patients; and (b) to evaluate the effectiveness of selected intervention methods in preventing learned food aversions in cancer patients receiving GI toxic chemotherapy.

5. OTHER DIETARY STUDIES

169. DIETARY STUDIES

Thomas, E. D., Fred Hutchinson Cancer Research Center, *1124 Columbia St., Seattle, Washington*, 98104, United States of America

This is part of a broader project. A summary of this subproject is not available.

170. DIETARY FIBER AND CANCER OF THE BOWEL IN THE RAT

Tasman Jones, C., Cochrane, L., Auckland University, School of Medicine, Dept. of Medicine, *P.O. Box 2175, Auckland, New Zealand*

OBJECTIVE: To ascertain if specific components of dietary fiber affect the internal environment of the gut in such a way that intestinal malignancy may be reduced.

APPROACH: Weanling DA rats maintained in wire cages have been offered diets of: low fat and no fiber; high fat, no fiber; high fat cellulose; high fat, pectin; high fat, galactomannan; high fat, tannin. After 26 weeks on this diet the rats are sampled and the mucosa examined morphologically. The internal milieu of the intestine, examined for bacterial enzymes

shown in epidemiological studies to be associated with a high incidence of cancer, and the stools are examined by the Ames test for the presence of carcinogens.

PROGRESS: The basic biochemical and morphological tests have been established. Because of a failure to get sufficient rats from the first mating of our rats, two groups of rats have been established. The first group has now completed its 26 weeks and samplings have just been obtained, but currently no data are available from these. The second group will complete their 20-week course in July. (Our original intention to feed dimethylhydrazine had to be abandoned when the facilities for such care of carcinogen-treated rats suddenly became unavailable.)

171. PHYSICAL AND BIOLOGICAL PROPERTIES OF DIETARY FIBERS (HUMAN, CATTLE)

Van Soest, P. J., Cornell University, Ithaca Campus, New York State College of Agriculture & Life Sciences, Dept. of Nutritional Sciences, *Ithaca, New York*, 14850, United States of America

This is part of a broader project. A summary of this subproject is not available.

B. THERAPEUTIC SUPPORT

1. HYPERALIMENTATION AND VITAMIN THERAPY

172. EFFECT OF PARENTERAL HYPERALIMENTATION IN ADVANCED NEOPLASMS

Thigpen, J. T., University of Mississippi, Medical Center, School of Medicine, Dept. of Medicine, *2500 N. State St., Jackson, Mississippi*, 39216, United States of America

This is part of a broader project. A summary of this subproject is not available.

173. HYPERALIMENTATION IN CANCER PATIENTS

Nixon, D. W., Emory University, School of Medicine, Dept. of Medicine, *1364 Clifton Rd. N.E., Atlanta, Georgia*, 30322, United States of America

This is part of a broader project. A summary of this subproject is not available.

174. HYPERALIMENTATION IN CANCER PATIENTS

Isacoff, W. H., University of California, Los Angeles Campus, Los Angeles County Harbor General Hospital, *1000 W. Carson St., Torrance, California*, 90509, United States of America

This is part of a broader project. A summary of this subproject is not available.

175. PARENTERAL HYPERALIMENTATION AND CHEMOTHERAPY FOR ADVANCED MALIGNANT NEOPLASMS

Thigpen, J. T., University of Mississippi, Medical Center, School of Medicine, Dept. of Medicine, *2500 N. State St., Jackson, Mississippi*, 39216, United States of America

This is part of a broader project. A summary of this subproject is not available.

176. ABNORMAL RESPONSE OF CANCER PATIENTS TO HYPERALIMENTATION

Nixon, D. W., Emory University, School of Medicine, Dept. of Medicine, *1364 Clifton Rd. N.E., Atlanta, Georgia*, 30322, United States of America

This is part of a broader project. A summary of this subproject is not available.

177. PHASE II STUDIES IN GASTROINTESTINAL CANCER

Moertel, C. G., Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

Studies will be performed on a minimum of forty patients per year with either pancreatic or gastric cancer and an additional forty patients with colorectal cancer. Contractor facilities will be adequate for approximately ten inpatients, space for outpatient visits, laboratories, and offices. Patients treated will be provided bed, nursing and laboratory services, drugs, and supplies consistent with a good clinical research unit. Participation and interest by surgery, radiology, clinical pathology, and medical departments is necessary for performance of these Phase II studies. In addition, the Contractor will have adequate knowledge of nutritional derangements related to GI cancer and its treatment and must have capabilities to provide hyperalimentation or other supportive care measures to control nutritional imbalances.

178. PHASE II STUDIES IN GASTROINTESTINAL CANCER

Schein, P. S., Georgetown University, School of Medicine, Dept. of Medicine, *3800 Reservoir Rd. N.W., Washington, District of Columbia*, 20007, United States of America

OBJECTIVES: Furnish services, qualified personnel, and material, equipment, and facilities as needed to conduct Phase II studies in gastrointestinal cancer. Participation and interest by surgery, radiology, clinical pathology, and medical departments is necessary for performance of these Phase II studies. In addition, the Contractor shall have adequate knowledge of nutritional derangements related to GI cancer and its treatment, and must have capabilities to provide hyperalimentation or other supportive care measures to control nutritional imbalances.

179. ADJUVANT EFFECTS OF ANTIOXIDANTS IN CANCER AND AGING

Baumgartner, W. A., Blahd, W. H., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Research Service, *Wilshire & Sawtelle Blvds., Room 209, Los Angeles, California*, 90073, United States of America

The primary objective of our study is to investigate whether the adjuvant properties of vitamin C, vitamin E, and selenium, established in healthy animals, can be applied towards the prevention or alleviation of tumor-induced depression of immunity (malignant energy), and whether such improvements in immunity result in an increased survival.

The start of our program was somewhat delayed by a 'freeze' of research funds which lasted until December 1979. Therefore the only laboratory work performed in 1979 was a search for a tumor model for malignant energy suitable for studying vitamin E and selenium effects. We investigated the suitability of Ehrlich ascites tumors maintained in Swiss Webster mice, using the dinitroflourobenzene skin sensitization assay for T-cell function. The classical method and a new isotopic method were used. Both assays showed that Ehrlich ascites tumors did not cause malignant anergy.

On completing the equipping of our laboratory in early 1980, we investigated a guinea pig tumor model, since this permits also the studying of vitamin C effects. The tumor model used was a Line 10 hepatocarcinoma, which is maintained in the rare syngeneic strain 2 guinea pig. Special animal facilities were constructed in our laboratory to protect our immunodepressed tumor bearing animals from the adverse effects of pathogenic organisms. Using the classical dinitrofluorobenzene skin sensitization test we showed that the tumor bearing guinea pigs suffered from malignant anergy. Experiments are currently in progress to test whether immunity and survival can be beneficially influenced by antioxidant supplementation.

180. CASE-CONTROL STUDY OF LUNG CANCER AND DIETARY VITAMIN A

Kolonel, L. N., Hinds, M. W., Nomura, A. M., Hankin, J. H., Lee, J., University of Hawaii System, Manoa Campus, Pacific Biomedical Research Center, Epidemiology Program, *2538 The Mall, Honolulu, Hawaii*, 96822, United States of America

This case-control study will test the hypothesis that dietary vitamin A may be protective against the development of lung cancer.

We will take advantage of the multiethnic population of Hawaii, with its dietary heterogeneity, to interview 500 newly diagnosed patients with primary lung cancer. These patients will be identified through the seven major hospitals on Oahu and will be men and women of Japanese, Caucasian, Filipino, Chinese and Hawaiian ethnic groups. For each lung cancer patient, two age- and sex-matched controls will be identified using the random-digit dialing method. Both cases and controls will be interviewed in their homes by trained multilingual interviewers, using a questionnaire designed to elicit quantitative information on the consumption of a large number of dietary items containing preformed vitamin A and vitamin A precursors. A detailed

smoking history and history of exposure to occupational lung carcinogens will also be part of the questionnaire.

The data will be analyzed to determine the dietary vitamin A consumption of cases and controls with adjustment for smoking and occupational history. Further analysis will determine the dietary vitamin A consumption of cigarette-smoking cases versus cigarette-smoking controls with adjustment for covariates. The demonstration of a relatively low dietary vitamin A intake among lung cancer patients, particularly among those who are smokers, would suggest that the incidence of this very common cancer might be reduced by increases in vitamin A intake.

BIBLIOGRAPHIC REFERENCES: Kolonel, L.N. Smoking and Drinking Patterns among Five Ethnic Groups in Hawaii. In: Second Symposium on Epidemiology and Cancer Registries in the Pacific Basin, Maui, January, 1978, Natl. Cancer Inst. Monograph 53:81-87, 1979. Hinds, M.W. and Kolonel, L.N. Malignant melanoma of the skin in Hawaii, 1960-1977. Cancer 45:811-817, 1980.

181. CANCER AND VITAMIN A

Ong, D. E., Page, D. L., Vanderbilt University, School of Medicine, Dept. of Biochemistry, *21st Ave. S. & Garland, Nashville, Tennessee*, 37232, United States of America

The proposed research is designed to contribute to the understanding of the prophylactic and therapeutic action of vitamin A and synthetic analogues on some neoplasms. Specific attention will be given to the cellular binding proteins for vitamin A, particularly from humans. The main objectives will be to develop antibodies against human binding proteins for radioimmunoassay and immunolocalization. These methods will be used to characterize human cancers and precancerous states. Techniques will be developed in model rat systems.

182. VITAMIN A

Meyskens, F. L., University of Arizona, School of Medicine, Dept. of Internal Medicine, *1501 N. Campbell Ave., Tucson, Arizona*, 85721, United States of America

The overall goals of this research are (1) to define the interaction of vitamin A and its synthetic derivatives (retinoids) with preneoplastic and neoplastic states. Our approach is to use advanced technology in a multidisciplinary nutritional cancer research effort in studies of retinol and retinoic acid binding proteins, polyamine biosynthesis and ornithine decarboxylase metabolism, cellular nutrition and transcription, zinc metabolism, DNA replication, immunological effects, hepatic injury, pharmacokinetics, tumor biology, and clinical oncology.

These studies will help identify the potential nutritional support that vitamin A and its derivatives might have in relation to cancer.

183. NUTRIENT DEFICIENCIES AND THE IMMUNE RESPONSE

Anthony, L. E., University of Texas, Health Science Center at Houston, School of Medicine, Dept. of Surgery, *Box 20036 Houston, Texas*, 77025, United States of America

Animal models for protein-calorie malnutrition and vitamin A deficiency using defined diets and experimental conditions will permit the isolation and evaluation of the influence of individual nutrients on a number of immune parameters. To evaluate whether secondary changes in nutrient metabolism or retention may contribute to changes in immunocompetence, the serum and liver levels of protein, vitamin A, vitamin B6, zinc and copper will be measured. In addition, inbred female rats chronically protein-malnourished will be infused with a total parenteral nutrition solution to assess the adequacy of that solution to promote immunocompetence. Rats will be assessed in vivo for their ability to mount a pure delayed hypersensitivity response to asobenzearsonate-tyrosine and for their ability to produce circulating antibodies to allogeneic sheep red blood cells. Lymphocytes from normal and malnourished rats will be compared with regard to (1) their ability to produce antibody, (2) their response to mitogen stimulation, and (3) their ability to respond to allogeneic cells. This approach, using both in vivo and in vitro assessment of immune competence, will provide new data concerning the etiology of the immune response and, potentially, optimal treatment of patients with infections and cancer who are further compromised by malnutrition.

184. EASTERN COOPERATIVE ONCOLOGY GROUP

Lerner, H. J., Zaren, H., Pennsylvania Hospital, Section of Surgical Oncology & Cancer Chemotherapy, *8th & Spruce Sts., Philadelphia, Pennsylvania*, 19107, United States of America

The summary for this project is under entry no. 110.

2. GENERAL NUTRITIONAL THERAPY

185. OPTIMAL NUTRITION FOR THE JAPANESE TO PREVENT CANCER

Kagawa, Y., Ebihara, A., Hamamoto, T., Jichi Medical School, Dept. of Biochemistry, *3311-1 Yakushiji, Minami kawachi-machi, Tochigi-ken 32904, Japan*

The Japanese are very different from Caucasians in their incidence of stomach cancer, breast cancer, etc. This may be due to differences in dietary habits, genetic factors, etc. The incidence of cancers of the stomach and uterine cervix is now rapidly decreasing in Japan, perhaps owing to the impact of westernization. However, breast and colon cancers is increasing. Optimal nutritional conditions which will keep death rates as low as possible will be sought by means of medical and ecological surveys carried out in remote parts of Japan where people live long and traditional customs are still observed, since there have been dramatic changes in the life styles and dietary habits of the Japanese. Statistical data on the average Japanese will be used as control. Nutrition is assessed by the National Survey which annually samples 10,000 randomly selected households for a three-day period. A district in Okinawa is followed closely, as are students of Jichi Medical School, in relation to dietary habits and disease.

186. NUTRITION AS AN ADJUNCT TO CHEMOTHERAPY IN LUNG CANCER

Feld, R., Ontario Cancer Inst., *500 Sherbourne St., Toronto, Ontario*, M4X 1K9, Canada

The study will determine how nutritional support given during chemotherapy affects tumor response and patient survival in patients with advanced small cell anaplastic carcinoma of the lung.

187. STUDY OF NUTRITION AS AN ADJUNCT TO CHEMOTHERAPY IN LUNG CANCER

Moran, E., University of California, Irvine Campus, California College of Medicine, Dept. of Medicine, *Irvine, California*, 92664, United States of America

The study will determine how nutritional support given during chemotherapy affects tumor response and patient survival in patients with advanced small cell anaplastic carcinoma of the lung.

188. PARENTERAL NUTRITION AND CHEMOTHERAPY IN LUNG CANCER

Clamon, G., University of Iowa, School of Medicine; Dept. of Internal Medicine, *Jessup Hall, Iowa City, Iowa*, 52240, United States of America

This study will determine how nutritional support given during chemotherapy affects tumor response and patient survival in patients with advanced small cell anaplastic carcinoma of the lung.

189. STUDY OF NUTRITION AS AN ADJUNCT TO CHEMOTHERAPY IN LUNG CANCER

Blum, R. H., New York University, School of Medicine, Dept. of Medicine, *550 1st Ave., New York, New York*, 10016, United States of America

This study will determine how nutritional support given during chemotherapy affects tumor response and patient survival in patients with advanced small cell anaplastic carcinoma of the lung.

190. STUDY OF NUTRITION AS AN ADJUNCT TO CHEMOTHERAPY IN LUNG CANCER

Weiner, R. S., State University System of Florida, University of Florida, School of Medicine, Dept. of Medicine, *1600 Archer Rd., Box J-266, Gainesville, Florida*, 32610, United States of America

The study will determine how nutritional support given during chemotherapy affects tumor response and patient survival in patients with advanced small cell anaplastic carcinoma of the lung.

191. EFFECTIVE CANCER THERAPY WITH NUTRITIONAL SUPPORT

Weiner, R. S., Cerda, J. J., Bailey, L. B., Roessler, G. S., Guild, R., State University System of Florida, University of Florida, School of Medicine, Dept. of Medicine, *1600 Archer Rd., Box J-266, Gainesville, Florida*, 32610, United States of America

This prospective, randomized clinical trial of nutritional support will utilize a uniform intensive combination chemotherapy regimen for induction of remission in patients with extensive oat cell lung cancer. The effects of intensive chemotherapy alone or with nutritional repletion will be measured in terms of a) tumor response, b) hematologic and immunologic tolerance to chemotherapy, c) response in clinical parameters of nutritional status, d) response in metabolic balance studies, and e) response in lean body mass by 40K measurements in a whole body counter. Sequential quantification of cell mediated immunity and hematopoietic function by in vitro assays of cell mediated lympholysis and of granulocyte progenitor cellS (CFU-C) in the peripheral blood will establish the effect of nutritional repletion on T cell and hematopoietic stem cell function. Laboratory and clinical data on sufficient numbers of patients will be collected over a two-month period of intensive therapy to establish significant correlation between clinical response and quantitative physiological and function assays. This study will define the role of adjunctive nutritional support of patients undergoing intensive anti-cancer therapy and will investigate the biochemical, metabolic, and cellular mechanisms by which nutrition and anti-cancer therapy interact.

192. POTENTIAL OF HOME TOTAL PARENTERAL NUTRITION DURING CANCER CHEMOTHERAPY

Burchenal, J. H., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

193. NUTRITIONAL SUPPORT AS AN ADJUNCT TO CANCER THERAPY

Hayes, D. M., Children's Hospital of Los Angeles, *4650 Sunset Blvd., Los Angeles, California*, 90054, United States of America

This is part of a broader project. A summary of this subproject is not available.

194. NUTRITIONAL REHABILITATION IN HEAD AND NECK CANCER

DeCosse, J. J., Memorial Hospital for Cancer & Allied Diseases, Dept. of Surgery, *1275 York Ave., New York, New York*, 10021, United States of America

The objective of the proposed randomized trial is to compare two methods of providing nutritional rehabilitation to patients with advanced head and neck cancer: intensive nasogastric tube feeding vs. optimal oral nutrition. The overall goal is to evaluate the effects of aggressive nutritional support on the patient's ability to tolerate and respond to radiation therapy and, in some cases, chemotherapy, as well as its effects on recurrence and survival.

Questions to be studied include differences in caloric and protein intake, weight, amount and duration of therapy, and severity of reactions to therapy; taste and smell impairment during therapy; the pattern of recovery of taste and smell following therapy and the effects of zinc therapy on this recovery; techniques for improving patient nutrition, both orally and extraorally; and the long-term consequences of aggressive nutritional support during short-term therapy.

Patients will be randomized into two groups: one will receive optimal oral nutrition and the other nasogastric feedings in addition to optimal oral nutrition. Both groups will receive support for an 11-week period. Thereafter, both groups will receive identical oral nutritional support for a two-year follow-up period.

Patients in both groups will also be randomized into groups receiving zinc therapy or a placebo to assess the role of zinc in the recovery of taste.

195. NUTRITION SUPPORT OF CHILDREN WITH WILMS' TUMORS

Rickard, K. A., Baehner, R. L., Grosfeld, J. L., Indiana University, Indiana University - Purdue University at Indianapolis, School of Medicine, Dept. of Nutrition & Dietetics, *1219 W. Michigan St., Indianapolis, Indiana*, 46202, United States of America

The early diagnosis and multimodal treatment of children with Wilms' tumors have vastly improved survival rates. However, severe malnutrition (PEM) and numerous complications and toxicity are often associated with the treatment. Malnutrition reduces the capacity to withstand aggressive treatment, increases susceptibility to opportunistic infections, depresses immune function and increases morbidity and mortality. The purpose of this study is to prospectively evaluate the benefits and complications of several modes of nutrition support (i.e., enteral nutrition, partial parenteral nutrition - PPN, peripheral nutrient infusion with enteral nutrition - and total parenteral nutrition - TPN, central nutrient infusion) in children (ages one to seven years) receiving multimodal treatment for Wilms' tumors, stages II-IV. Each regimen will be evaluated for its effectiveness in preventing or reversing PEM, maintaining or restoring immune competence, and obviating treatment modifications and complications. Children with stage II-IV Wilms' tumors who are considered malnourished at diagnosis will be randomized to receive either TPN or PPN throughout the period of irradiation. Nourished children with either stage IV or stage II/III and unfavorable histology Wilms' tumors will be randomized to receive either PPN or TPN throughout the six weeks of abdominal irradiation. Nourished children with stage II/III and favorable histology Wilms' tumors will receive either a comprehensive enteral nutrition program or PPN throughout the four weeks of intense treatment which includes abdominal irradiation. Thereafter, all children will receive a comprehensive enteral nutrition program to prevent subclinical PEM during 2, 3, or 4 drug chemotherapy maintenance programs. Nutritional state, immunological capacity, treatment modifications and complications will be evaluated at diagnosis and at 4, 6, 19, and 26 weeks during the initial, intense and maintenance periods.

196. PREVENTION AND REVERSAL OF MALNUTRITION IN NEUROBLASTOMA

Baehner, R. L., Rickard, K. A., Grosfeld, J. L., Matchett, N., Weetman, R. M., Provisor, A. J., Boxer, L. A., Oei, T. O., Indiana University, Indiana University - Purdue University at Indianapolis, School of Medicine, Dept. of Pediatrics, *1219 W. Michigan St., Indianapolis, Indiana*, 46202, United States of America

The prognosis for stage IV children with neuroblastoma is dismal. Aggressive multimodal treatment programs often result in severe malnutrition (PEM) which interferes with therapy and increases morbidity and mortality. The plan of this study is to evaluate the effectiveness of enteral and parenteral nutrition in preventing and/or reversing PEM, maintaining or restoring immune competence, preventing treatment delays, and improving tumor response of 36 children (ages one to six years) with metastatic neuroblastoma receiving chemotherapy (5 drugs: Cytoxan, vincristine, DTIC, adriamycin, VM-26) every three weeks. At diagnosis, children who are considered nourished at diagnosis will be randomized to receive either a comprehensive enteral nutrition program or total parenteral nutrition (TPN) for the first 35 days of treatment. Children considered malnourished at diagnosis will be randomized to receive either TPN or partial parenteral nutrition plus enteral nutrition for the first 35 days of the treatment. Thereafter, all children will receive a comprehensive enteral nutrition program. Nutritional status, recall skin test response, treatment delays and tumor response will be evaluated at 0, 6, 12, 18 and 22 weeks. Additional nutritional evaluations (dietary, anthropometric and biochemical) will be determined weekly during the first 5 weeks to identify nutritional indices of clinical and subclinical PEM in children undergoing treatment for metastatic neuroblastoma.

197. DIETARY TREATMENT OF BRAIN TUMORS (HUMAN)

Banks, W. L., Virginia Commonwealth University, Medical College of Virginia, Dept. of Biochemistry/Surgery, *1200 E. Broad St., Richmond, Virginia*, 23298, United States of America

This is part of a broader project. A summary of this subproject is not available.

198. NUTRITIONAL SUPPORT AND REHABILITATION FOR CANCER PATIENTS

Butterworth, C. E., Krumdieck, C. L., Weinsier, R. L., Mitchell, C., University of Alabama in Birmingham, School of Community & Allied Health, Dept. of Nutrition Sciences, *Tidwell Hall BOO6, University Station, Birmingham, Alabama*, 35294, United States of America

Observations made since the inception of this project in 1976 indicate a very high prevalence of nutritional complications among patients hospitalized for cancer. These include weight loss, protein-calorie malnutrition and multiple vitamin deficiencies. Until recently it was not possible to document the extent of these complications statistically, nor to provide information on the effectiveness of nutritional intervention. For obvious moral and ethical reasons it has not been possible to allow nutritional imbalance to remain untreated once it has been recognized.

It is now apparent that approximately one-half of patients with identifiable nutrition complications arising as a result of cancer or its therapy can receive significant benefit from aggressive nutritional intervention.

During the 1980/81 year, we propose to continue to develop means to identify and treat these patients. One goal is to make the assessment of nutritional status a part of every patient's evaluation. Another goal is to create enhanced physician awareness of the role of nutrition in support of cancer patients. A third goal is continued strengthening of a nutrition-support team to aid in delivery of specialized care. The fourth goal is to collect data for computerized storage, retrieval, and analysis to study correlations between nutrition parameters, therapy, and outcome.

199. NURSING INTERVENTIONS IN NUTRITION OF CANCER PATIENTS

Dixon, J. K., Moritz, D. A., Campbell, D., Sanderford, L., DeNicola, M., Yale University, School of Nursing, Program in Nursing Research, *310 Cedar St., New Haven, Connecticut*, 06510, United States of America

Persons with cancer often develop nutritional complications as a result of their disease or its treatment, and, in turn, nutritional deficiencies are known to diminish an individual's ability to tolerate therapies and to recover from the disease. Little is known concerning methods through which the quantity and quality of oral intake of the cancer patient can be augmented by the health professional. The objective of the proposed project is to conduct a clinical nursing experiment evaluating the effectiveness of two nursing interventions as reflected in the food intake patterns, nutritional status and activities of daily living of cancer patients. Respectively, these intervention protocols will involve emphasis on frequent nutritional supplements and preprandial relaxation techniques. Subjects will be followed over a sixteen-month period. The accuracy of the nutritional assessment methodology to be used will also be determined. The anticipated result of this project will be a preliminary system for assessing the malnourished or potentially malnourished cancer patient and prescribing subsequent nutrition interventions. Such a system may enable nurses to improve the nutritional well-being of cancer patients, thus enhancing their response to therapy and the quality of their lives.

200. NUTRITIONAL SUPPORT AS AN ADJUNCT TO CANCER THERAPY (HUMAN)

Mullen, J. L., University of Pennsylvania, School of Medicine, Dept. of Medicine/Surgery, *36th & Hamilton Walk, Philadelphia, Pennsylvania*, 19174, United States of America

This is part of a broader project. A summary of this subproject is not available.

201. OPTIMAL NUTRITIONAL SUPPORT AS ADJUNCT TO CANCER THERAPY

Donaldson, S. S., Stanford University, School of Medicine, Dept. of Pediatrics, *300 Pasteur Dr., Stanford, California*, 94305, United States of America

This project will be a multidisciplinary project coordinated with other DNCP projects in the clinical field to: determine whether optimal nutritional support alters the rate of tumor growth; determine whether optimal nutritional support alters the status of the pediatric cancer patient so that the patient's tolerance to antineoplastic therapy is increased and the efficacy of therapy is increased; determine whether specific antineoplastic therapy interferes with the efficacy of nutritional therapy, impairs utilization, or causes complications; and determine how optimal nutritional support affects the host-tumor response and host-immune response to cancer therapy.

202. OPTIMAL NUTRITIONAL SUPPORT AS ADJUNCT TO CANCER THERAPY

Watkins, J., Children's Hospital Medical Center, *300 Longwood Ave., Boston, Massachusetts*, 02115, United States of America

This project will be a multidisciplinary project coordinated with other DNCP projects in the clinical field to: determine whether optimal nutritional support alters the rate of tumor growth; determine whether optimal nutritional support alters the status of the pediatric cancer patient so that the patient's tolerance to antineoplastic therapy is increased and the efficacy of therapy is increased; determine whether specific antineoplastic therapy interferes with the efficacy of nutritional therapy, impairs utilization, or causes complications; and determine how optimal nutritional support affects the host-tumor response and host-immune response to cancer therapy.

203. OPTIMAL NUTRITIONAL SUPPORT AS AN ADJUNCT TO CANCER THERAPY

Hayes, D. M., Children's Hospital of Los Angeles, *4650 Sunset Blvd., Los Angeles, California*, 90054, United States of America

This project will be a multidisciplinary project coordinated with other DNCP projects in the clinical field. This project will: determine whether optimal nutritional support alters the rate of tumor growth; determine whether optimal nutritional support alters the status of the pediatric cancer patient so that the patient's tolerance to antineoplastic therapy is increased and the efficacy of therapy is increased; determine whether specific antineoplastic therapy interferes with the efficacy of nutritional therapy, impairs utilization, or causes complications; and determine how optimal nutritional support affects the host-tumor response and host-immune response to cancer therapy.

204. OPTIMAL NUTRITIONAL SUPPORT AS ADJUNCT TO CANCER THERAPY

Samuels, M. L., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas*, 77030, United States of America

This project will be a multidisciplinary project coordinated with other DNCP projects in the clinical field. This project will determine whether optimal nutritional support alters the status of the adult cancer patient so that the patient's tolerance to antineoplastic therapy is increased and the efficacy of therapy is increased.

205. OPTIMAL NUTRITIONAL SUPPORT AS ADJUNCT CANCER THERAPY

Steffee, W. P., University Hospital Inc., *75 E. Newton St., Boston, Massachusetts*, 02118, United States of America

OBJECTIVES: Determine whether optimal nutritional support alters the rate of tumor growth; determine whether optimal nutritional support alters the status of the adult cancer patients so that the patient's tolerance to antineoplastic therapy is increased and the efficacy of therapy is increased; determine whether specific antineoplastic therapy interferes with the efficacy of nutritional therapy, impairs utilization or causes complications; and determine how optimal nutritional support affects the host-tumor response and host-immune response to cancer therapy.

206. OPTIMAL NUTRITIONAL SUPPORT AS ADJUNCT TO CANCER THERAPY

Blackburn, D., New England Deaconess Hospital, *185 Pilgrim Rd., Boston, Massachusetts*, 02215, United States of America

OBJECTIVES: Determine whether optimal nutritional support alters the rate of tumor growth; determine whether optimal nutritional support alters the status of the adult cancer patient so that the patients's tolerance to antineoplastic therapy is increased and the efficacy of therapy is increased; determine whether specific antineoplatic therapy interferes with the efficacy of nutritional therapy, impairs utilization or causes complications; and determine how optimal nutritional support affects the

host-tumor response and host-immune response to cancer therapy.

207. OPTIMAL NUTRITIONAL SUPPORT AS ADJUNCT TO CANCER THERAPY

Nixon, D. W., Emory University, School of Medicine, Dept. of Medicine, *1364 Clifton Rd. N.E., Atlanta, Georgia*, 30322, United States of America

The contractor shall furinsh services, qualified personnel, and material equipment, as well as facilities, not otherwise provided by the Government under the terms of this contract, as needed to perform the work set forth.

208. NUTRITIONAL INTERVENTION IN CANCER CHEMOTHERAPY

Hilton, M. A., Hoffman, J. L., University of Louisville, School of Medicine, Dept. of Biochemistry, *101 W. Chestnut, Louisville, Kentucky*, 40202, United States of America

We propose a protocol to 'rescue' lymphoma-bearing mice from lethal doses of the anti-cancer drug, methotrexate (MTX) with N5-methyltetrahydrofolate (N5-CH3-FH4) when the animals are maintained on a methionine-free diet containing DL-homocystine as the only sulfur amino acid. We present evidence from the literature and from our own preliminary experiments which supports the concept that the regimen we propose may provide selective 'rescue' of normal cells in the presence of the L-1210 and L-5178Y neoplastic cells, which are known to be methionine-dependent.

We have outlined the studies on whole animals which will be required to refine our protocol so that we may contrast tumor growth in treated and untreated animals. We shall also measure in the tumors the activities of enzymes involved in pathways in sulfur amino acid metabolism, i.e., methionine synthetase, cystathionase, and glycine N-methyltransferase.

By exploring the molecular basis for the observed tumor growth in whole animal experiments we shall be expanding current understanding of the comparative biochemistry and sensitivity to MTX of these lymphoma cells. The knowledge obtained by the proposed research could lead to the use of nutritional manipulation as an adjuvant to established cancer chemotherapy programs.

209. INFLUENCE OF NUTRITION AFTER CANCER THERAPY

Sensenbrenner, L. L., Stuart, R. K., Johns Hopkins University, School of Medicine, Dept. of Medicine, *725 N. Wolfe St., Baltimore, Maryland*, 21205, United States of America

We plan to investigate the effect of acute periods of protein deprivation on the ability of a lymphohematopoietic system injured by systemic cancer therapy to repair and restore itself. Our preliminary studies of the ability of transplanted bone marrow to repopulate a lethally irradiated mouse have demonstrated that in the presence of no protein intake, there is marked suppression of hematopoiesis. The studies proposed herein will examine the quantitative effect of graded doses of dietary protein on the restoration of normal repopulation kinetics of transplanted bone marrow. Studies will also be carried out to examine quantitatively the effect of graded amounts of dietary protein on the ability of autologous residual bone marrow CFUs and CFUc to repopulate the mouse after sublethal systemic chemotherapy and irradiation. Using the adoptive transfer system, we will determine quantitatively the effect of those same protein deficient diets on the ability of syngeneic immunocompetent cells to recover. These studies will be extended to the study of the replicative ability of CFUs, CFUc, and their progeny from murine bone marrow cultured in diffusion chambers implanted into mice maintained for a short period of time on graded protein diets. Marrow from normal humans and patients with leukemia in varying states of remission and relapse will be grown in diffusion chambers implanted into chemotherapy and/or radiation treated mice that are subjected to dietary manipulation. The effect of these diets on the chamber total and differential cell count as well as the content of CFUc will be determined.

210. DIET AND L-DOPA METHYL ESTER THERAPY OF MELANOMA

Meadows, G. G., Washington State University, School of Pharmacy, *Pullman, Washington*, 99163, United States of America

The proposed research deals with some amino acid requirements for growth of B-16 melanoma in mice. The dietary intake of methionine and cysteine will be correlated with the establishment of tumors and also with the effect on growth of established tumors in BDF1 mice. Recent studies suggest that this tumor system has a requirement for cysteine since many melanoma cell lines in vitro are unable to grow without this preformed amino acid.

The anti-tumor effect of L-dopa methyl ester and carbidopa in combination with dietary manipulation of methionine and/or cysteine will also be studied. It is known that L-dopa depletes the tumor of cysteine.

During metastasis of melanomas, elevation in serum and urinary cysteinyldopa occurs. This compound will be monitored in mice on the various diet and drug combinations in order to gain further insight into the importance of this metabolite to growth and metastasis of B-16 melanoma.

211. NUTRITION - A POSSIBLE CORRECTIVE APPROACH TO METHOTREXATE HEPATOTOXICITY

Barak, A. J., Sorrell, M. F., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *4101 Woolworth Ave., Omaha, Nebraska*, 68105, United States of America

Methotrexate (MTX), a folate antagonist widely used in treatment of psoriasis and neoplatic diseases, has been shown to be hepatotoxic in humans. The mechanism for this hepatotoxicity is unknown.

Male Sprague-Dawley rats (200g) were injected i.p. with 0.1 mg MTX per kg per day over a time course of 1, 2 and 4 months. Despite the fact that it was shown that the drug inhibited hepatic dihydrofolic acid reductase (DHFA reductase) levels by 85%-90% at each time period, the animals showed normal growth and lack of fatty infiltration in the liver throughout the experimental period. In line with the inhibition of DHFA reductase, examination of the liver showed that the levels of N5-methyltetrahydrofolic acid, the prime methylator in the conversion of homocysteine to methionine, had decreased by 50% at the 2 and 4 month periods. Analysis (using a method developed in this laboratory, Lipids 14:860-863, 1979) for levels of hepatic betaine, a secondary methylator in the conversion of homocysteine to methionine appeared to mirror the N5methyltetrahydrofolic acid levels with significant decreases occurring at the 2 and 4 month periods.

These results suggest that in the rat, where hepatic choline oxidase exists at elevated levels and where the production of betaine should be high, the betaine may be utilized as a compensating methylator when folate metabolism is antagonized by MTX and protect the rat from the toxic effects of this drug.

212. NUTRITION AND MAMMARY CARCINOGENESIS

Thompson, H. J., Stackhouse, L. J., Mehta, R., University System of New Hampshire, University of New Hampshire, School of Life Sciences & Agriculture, Dept. of Home Economics, *Durham, New Hampshire*, 03824, United States of America

Studies are proposed to determine a nontoxic level and source of dietary selenium which affords maximal protection against 1-methyl-1-nitrosourea and 7,12-dimethylbenz (alpha) anthracene-induced mammary carcinogenesis. The inhibitory effect of selenium on the initiation and progression stages of carcinogenesis will be studied both in mammary gland organ culture and via feeding studies. The role of alterations in both the metabolism of steroid sex hormones and the synthesis of DNA and protein will be investigated as possible mechanisms by which selenium exerts its effect. Additional studies will be conducted to answer questions pertinent to the application of selenium treatment to breast cancer control and prevention.

C. BIOCHEMISTRY AND METABOLISM OF NUTRIENTS

213. A STUDY OF PROTEIN TURNOVER IN MALIGNANT DISEASE

Harrison, R., Kark, A. E., Halliday, D., Garrow, J., Clinical Research Centre, Oncology Unit, *Watford Rd., Harrow, Middlesex, United Kingdom*

OBJECTIVES: a) To assess the reproducibility of measurements of protein turnover as made by the N15 glycine/

urinary ammonia method. b) To assess the application of this method to clinical studies in malignant disease.

APPROACH: a) Factors affecting the reproducibility of the method will be investigated on normal volunteers, under controlled dietary conditions. The dietary requirements will be assessed using an Oxylog measurement of oxygen consumption. b) Alterations in protein turnover in patients with malignant disease are studied in inpatients on a controlled diet matched to their measured oxygen consumption. The duration of the study period varies between 3 and 14 days. The longer study period is used only in patients undergoing hyperalimentation. Some patients are studied for a second period either in the immediate post-operative period or at an interval after surgery. In order to attempt to assess protein metabolism in terms of variations in synthesis and breakdown a measurement of protein turnover must be made. Until recently the methodology employed was cumbersome, and the use of C14 prevented serial studies. The method involves a tracer dose of N15 glycine given by mouth, and the cumulative N15 enrichment of urinary ammonia is measured, as is total urinary ammonia excretion over a 12-hour period. This method is non-invasive and requires less patient cooperation than other methods. This study demonstrated a reproducibility of plus or minus 13%. If we are able to show an equivalent or improved reproducibility, this method would be a useful additional means of evaluating protein metabolism in clinical studies.

PROGRESS: Initial control studies using the N15 glycine/12-hour ammonia method showed wide variation, unsuitable for clinical studies. We are therefore undertaking a series of control studies to establish if it is possible, by applying more stringent experimental conditions, including total dietary control, to standardize physical activities during the experimental period to improve the reproducibility of this method.

214. PROTEIN NUTRITION AND PRIMARY ACTION OF A CARCINOGEN

von der Decken, A., Eriksson, B., Wenner Gren Inst. for Experimental Biology, Dept. of Cell Physiology, *Norrtullsgatan 16, S11345 Stockholm, Sweden*

Nitroso compounds show great versatility as carcinogenic agents. Knowledge about dietary protection from the carcinogenic action of nitroso compounds is of prevailing interest in relation to carcinogenesis in humans. The aim of this investigation is to study the effect of administration of dimethylnitrosamine to mice fed a diet balanced in amino acids, or proteins enriched in sulfur-containing amino acids. The dietary conditions used will include high quality proteins at a 20% level and enrichment of the proteins with the sulfur-containing amino acids methionine and cysteine. These are introduced to test the theory that a reaction of the sulfur groups with dimethylnitrosamine intermediates will prevent interaction with the susceptible DNA molecules. The objectve is to investigate the protective influence that such a diet has on the occurence of single strand breaks in DNA caused by dimethylnitrosamine.

APPROACH: Quantitation of the breaks produced in DNA will be done by labeling with 125-iodine followed by separation of the denatured DNA in polyacrylamide gel electrophoresis and autoradiography. Labeling of DNA at the break points with gamma-32P-ATP and polynucleotide kinase (EC 2.7.1.78) will also be tested. DNA will be labeled at the free 5'OH group with 32P, and after separation by polyacrylamide gel electrophoresis radioactivity will be determined. A further step is formation of initiation complex for RNA synthesis with Escherichia coli RNA polymerase containing sigma factor (EC.2.7.7.6) and gamma-32P-ATP or gamma-32P-GTP as the initiation nucleotide. These may be replaced by 14C or 3H labeled ATP or GTP. The heparin resistant complex is precipitated, excess of radioactivity removed and the remaining radioactivity determined. A nonspecific initiation occurs in vitro at each single strand break.

215. METABOLIC HOST REACTIONS IN CANCER DISEASE

Schersten, T., Lundholm, K., Sahlgrenska Sjukhuset, Dept. of Surgery I, *S41345 Gothenburg, Sweden*

OBJECTIVE: To elucidate the tumor host reactions and analyze the mechanisms for the metabolic alterations of the host and thereby create a basis for adjunct metabolic therapy.

APPROACH: Analyses of energy balance during progression and treatment (nutritional and surgical) of tumor disease in man and experimental animals. Analyses of regulation mechanisms for protein turnover, glucose turnover and insulin sensitivity in tumor-bearing man and experimental animals.

PROGRESS: The role of the decreased caloric intake, as a result of anorexia, in the metabolic host reactions has been studied in tumor-bearing mice (C-57, MCG 101). The decreased food intake cannot by itself explain the reactions in skeletal muscles and the liver. However, the decreased caloric intake contributes to the depressed protein synthesis and increased protein degradation rate in skeletal muscles. It also amplifies the hepatic metabolic reactions in the tumor-bearing animal. The importance of the immune reaction has been studied by intraperitoneal injections of antigens from Corynebacterium parvum in control mice. A considerable number of the tumor host reactions were induced by these injections. However, dissimilarities exist, which may be dependent on more specific tumor factors. Tumor-bearing mice showed a changed albumin turnover. The half-life was 20-24 hours in the tumor mice and 33-37 hours in controls. Evidence was obtained that the trigger of the changed turnover was localized to the degradative pathways. In human cancer the glucose pool of the body was expanded (1.15 plus or minus 0.23 g/kg) as compared to matched controls (0.5 plus or minus 0.07 g/kg). The glucose production was also increased (46.9 plus or minus 10 mmol/kg per day) in cancer patients (controls 22.7 plus or minus 2.7). By double-isotope techniques it could be shown that cancer patients had a significantly higher rate of cycling of glucose carbons, suggesting an altered futile cycling. Total parenteral nutrition of cancer patients increased the protein synthesis and the RNA content of skeletal muscles.

216. THE EFFECT OF DIFFERENT DIETS ON THE ACTIVITY OF THE ENZYME 9 DESATURASE IN EHRLICH ASCITES CELLS

de Tomas, M. E., Mercuri, O. F., Universidad Nacional de La Plata, Facultad de Ciencias Medicas, Inst. de Fisiologia, Cat. Bioquimica, *Calles 60 y 120, 1900 La Plata, Argentina*

OBJECTIVES: Neoplastic cells in general, and some hepatomas in particular, are shown to have a low activity of 9 desaturase, an enzyme important because of its function of transforming saturated acids into monoethyl acids. This work is designed to determine if the Ehrlich ascitic cells manifest a desaturating activity and if this activity can be regulated by nutrition.

METHODS: The composition of fatty acids of lipids in Ehrlich cells will be modified by feeding Swiss mice (which will then carry the tumor) diets of varying linoleic acid content for a period of 5 weeks.

The tumor will then be grown in the mice and the cells will be incubated with carbon-14-labelled palmitic acid or carbon-14-labelled acetate, and the saturation will be measured. At the time the composition of phospholipid fatty acids will be determined. Cell membranes will be separated and their desaturation will be measured.

217. ENERGY METABOLISM IN CANCER PATIENTS

Long, C. L., Blakemore, W. S., Merrick, H. W., Renk, C. M., Birkhahn, R. H., Medical College of Ohio at Toledo, School of Medicine, Dept. of Surgery, *Box 6190, Toledo, Ohio*, 43614, United States of America

This project is designed to quantitatively evaluate energy expenditure and the composition of the fuel mixture burned in patients with gastrointestinal cancer. In addition, glucose kinetics (oxidation rates, pool sizes, turnover rates and recycling) will be measured using 14C-U-L-glucose, the degree of gluconeogenesis will be measured using 14C-L-alanine, and whole-body protein synthesis and catabolic rates will be measured using 15N-L-alanine. These kinetic studies will be carried out at the beginning of the patient's hospital stay and during nutritional support before and after surgical removal of the tumor. Nutritional support will be high fat-low carbohydrate or high carbohydrate-low fat diet with constant protein composition.

The data should provide information on energy and substrate demands of the host and of the tumor by comparing the initial study (post-absorptive) with the pre-op study during nutritional support. Compartmentalization of the host to tumor demands may be ascertained by comparing the results before

and after surgical removal of the tumor employing the same nutritional intake baseline in both studies. The postoperative study will be conducted only when the surgical catabolic transients are absent, which will be confirmed by a number of measured responses.

It is hoped that these studies might provide additional information related to the amount and kind of nutritional support cancer patients should receive in their total care.

218. METABOLIC STUDIES IN TUMOR-BEARING PATIENTS AND ANIMALS

Brennan, M. F., Arbeit, J., Maher, M., Jones, D., Sloan, G., Burt, M. E., Shamberger, R. C., White, D., Gorschboth, C., Peters, M. L., Kirkemo, A., Saxe, A., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Surgical Metabolism Section, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

The Surgery Branch is vigorously involved in the assessment of the efficacy of total parenteral nutrition as a means of nutritional support of the cancer-bearing host. These studies utilize methodologies employing stable isotopes and labelled substrates to examine glucose and amino acid metabolism. Animal models are utilized for examination of gluconeogenesis and glucose kinetics. Particular efforts are directed at examining methods of host preservation and metabolic cost of antineoplastic therapy. Continued effort is being made in the elucidation of function of fresh and cryopreserved parathyroid and other endocrine tissues.

BIBLIOGRAPHIC REFERENCES: Lowry, S.F., Norton, J.A., and Brennan, M.F.: Glucose turnover and gluconeogenesis during hypocaloric glucose infusion in tumor-bearing animals. J. Natl. Cancer Inst. 64: 291-296, 1980. Burt, M.E., Norton, J.A., and Brennan, M.F.: The human tumor-bearing limb: An ex vivo model. Surgery 87: 123-132, 1980.

219. METABOLIC STUDY OF ADULT AND PEDIATRIC CANCER PATIENTS

Holroyde, C. P., Reichard, G. A., Axelrod, R. S., Skutches, C. L., Paul, P., Lankenau Hospital, Oncology Research Unit, *Lancaster & City Line Aves., Philadelphia, Pennsylvania,* 19151, United States of America

The overall objective of this research is to investigate glucose and lactate metabolism in hospitalized patients with malignant solid tumors, particularly colorectal cancer. Using isotope tracer infusion techniques, the production, utilization and oxidation of glucose and lactate will be measured under standardized conditions. The possible relationship between lactate production and tumor growth will be investigated by observations on the effect of cancer therapy on lactate metabolism. In addition, the host metabolic response to nutritional supplementation by short-term intravenous hyperalimentation will be evaluated in debilitated patients. This data may provide a rational basis for improvements in current therapy.

D. BROAD CLINICAL SUPPORT PROGRAMS AND FACILITIES

220. RESEARCH DIETETIC SECTION

Frankman, C., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Surgery, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas,* 77030, United States of America

This is part of a broader project. A summary of this subproject is not available.

221. SUPPORT FOR THE DIET, NUTRITION AND CANCER PROGRAM

Spargur, J., Capital Systems Group Inc., *6110 Executive Blvd., Suite 850, Rockville, Maryland,* 20852, United States of America

OBJECTIVE: Provide workshop, conference, and meeting support for the DNCP (a maximum of ten meetings per year are anticipated). This includes providing the necessary technical/scientific expertise to assist the Project Officer in selecting participants and in performing the individual tasks as listed, and the contractor maintaining appropriate liaison with the individuals, institutions, and organizations involved.

222. NUTRITION SUPPORT SERVICE

Mullen, J. L., University of Pennsylvania, School of Medicine, Dept. of Surgery, *36th & Hamilton Walk, Philadelphia, Pennsylvania,* 19174, United States of America

This is part of a broader project. A summary of this subproject is not available.

223. CLINICAL NUTRITIONAL FACILITIES

Butterworth, C. E., University of Texas, University of Texas System Cancer Center, M.D. Anderson Hospital & Tumor Inst., Dept. of Surgery, *6723 Bertner Ave., c/o Texas Medical Ctr., Houston, Texas,* 77030, United States of America

This is part of a broader project. A summary of this subproject is not available.

224. SPECIALIZED NUTRITION LABORATORY UNIT

Cornwell, P. E., University of Alabama in Birmingham, School of Community & Allied Health, Dept. of Nutrition Sciences, *Tidwell Hall BOO6, University Station, Birmingham, Alabama,* 35294, United States of America

This is part of a broader project. A summary of this subproject is not available.

225. DEVELOPMENT OF CLINICAL NUTRITION RESEARCH UNIT

Greene, H. L., Helinek, G., Borum, P., Folk, C., Schenker, S., O'Leary, J. P., Oldham, R., Meng, H. C., MacDonell, R. C., Vanderbilt University, School of Medicine, Dept. of Pediatrics, *21st Ave. S. & Garland, Nashville, Tennessee,* 37232, United States of America

Six clinical nutrition research projects serve as a focus for CNRU activity and include the following studies: 1) Nutritional factors in hepatic encephalopathy. 2) Optimal intake of zinc and copper in pediatric patients requiring total parenteral nutrition or defined formula diets. 3) Micronutrient metabolism in patients with essential fatty acid deficiency. 4) Preliminary assessment of the efficacy of supplemental enteral tube feedings as an adjunct to combination chemotherapy in patients with small cell and anaplastic carcinoma of the lung. 5) Effects of chronic dialysis and uremia on vitamin and trace element metabolism in children and adults. 6) Nutritional assessments as predictors for determining need for special nutritional support in presurgical patients. Additionally, a pilot study to develop and utilize accurate, inexpensive, and timely screening tools for identifying undernourished hospital patients at admission is in progress. A brief nutrition questionnaire, the height-weignt index, and computerized screening of potentially nutrition-related routine laboratory data serve as the basis for screening of all admissions. The CNRU Metabolic Assessment Lab is developing age- and sex-related normal ranges for vitamin, mineral, and functional protein assays. Schemas have been devised for each project and the Clinfo computer system is in use for the storage and analysis of data.

226. CORE CLINICAL NUTRITION RESEARCH CENTER

Butterworth, C. E., Krumdieck, C. L., Navia, J. M., Weinsier, R. L., Laven, G. T., Cornwell, P. E., Craig, C. B., Moore, J. E., Doleys, D. M., Baggott, J. E., Eto, I., Mitchell, C., University of Alabama in Birmingham, School of Community & Allied Health, Dept. of Nutrition Sciences, *Tidwell Hall BOO6, University Station, Birmingham, Alabama,* 35294, United States of America

This is a proposal to organize a Comprehensive Clinical Nutrition Research Unit or 'Center'. The present department of Nutrition Sciences, supported jointly by three Schools (Community and Allied Health, Medicine, and Dentistry) will coordinate the interdisciplinary program.

Our objectives are improved patient care and disease prevention through: (a) better utilization of existing knowledge about nutrition, and (b) research to develop better methods for nutritional assessment, data analysis and health care delivery.

We propose to create a unifying administrative unit along with three other centralized units or teams: (1) a laboratory to provide shared facilities for basic research and clinical support services, (2) a clinical nutrition support team, and (3) an international unit to promote understanding and exchange of information with students and scientists in other parts of the world. Although each component has identifiable major responsibilities, extensive interaction and collaboration will be required of them.

The organization is designed to provide maximal efficiency of research, service, and training through enhanced personal contact, greater intellectual stimulation, use of shared resources, and coordinated effort.

227. COOPERATIVE CORE LAB AND CLINICAL NUTRITION RESEARCH

Rivlin, R. S., Memorial Hospital for Cancer & Allied Diseases, *1275 York Ave., New York, New York*, 10021, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

IV. PAIN MANAGEMENT OF CANCER PATIENTS

228. PALLIATIVE TREATMENT OF ESOPHAGEAL CARCINOMA WITH RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY

Brunet, R., Richaud, P., Lagarde, C., Durand, M., Fondation Bergonie, Dept. of Medicine, *180, rue de Saint-Genes, 33076 Bordeaux, France*

OBJECTIVES: 1) To determine if chemotherapy given before radiotherapy improves the results of treatment in non-surgical esophageal carcinomas. 2) To compare limited and large field radiotherapy in the same cancers.

APPROACH: Patients with non-resectable squamous cell esophageal carcinoma without metastasis are available for this trial. They are randomly allocated to receive one of the following three treatments: 1) large field radiotherapy alone; 2) chemotherapy followed by large field radiotherapy; or 3) chemotherapy followed by limited radiotherapy.

PROGRESS: A preliminary historical study was in favor of combination of the two treatments in 22 patients treated by radiotherapy plus chemotherapy. In November 1978, 15 patients were included in the present randomized trial.

229. CURATIVE AND PALLIATIVE TREATMENT OF COLORECTAL CANCER AND ITS EFFECT ON QUALITY OF LIFE

Bjurulf, P., Sjodahl, R., Wretmark, G., Alinder, J., Blomquist, C., Gregersen, N. P., Hartvig, B. O., Nilsson, E., Regionsjukhuset, Dept. of Surgery, Preventive & Social Medicine, Psychiatry, *58185 Linkoping, Sweden*

In evaluation of effects of treatment on colorectal cancer, time from diagnosis to death has mainly been used as a criterion.

This project aims at a broader estimation of the patient's situation, including activities of daily living, social functions, psychological reactions and reactions of close relatives during different stages of the disease.

Such a comprehensive instrument will provide a better basis for evluation of new forms of therapy, especially with regard to palliative treatment.

230. THERAPY OF PATIENTS WITH GASTRIC CARCINOMA

Holyoke, E. D., State Dept. of Health, *Empire State Plaza, Tower Bldg., Albany, New York*, 12237, United States of America

The employment of multiple therapeutic modalities in treatment of resectable, unresectable and disseminated gastric carcinoma to increase the rate of cure, survival and palliation is undertaken. Since chemotherapy and radiation therapy can destroy the disseminated cancer cells and local microscopic foci of tumor, both modalities are used singly and in combination in treatment. These studies continue.

231. ADVANCED BREAST CANCER - A CONTROLLED TRIAL OF THE PALLIATIVE TREATMENT OF PLEURAL EFFUSIONS

Fentiman, I. S., Rubens, R. D., Hayward, J. L., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

A controlled trial is in progress in which patients with previously untreated pleural effusions are being allocated randomly to one of two treatment methods, either mustine pleurodesis or talc poudrage. The trial aims to determine which technique is better for management of pleural effusions in patients with advanced breast cancer.

232. ADVANCED BREAST CANCER - A RETROSPECTIVE ANALYSIS OF PATIENTS DEVELOPING CEREBRAL METASTASES

Sparrow, G. E., Rubens, R. D., Imperial Cancer Research Fund, Breast Cancer Unit, *Lincoln's Inn Fields, London WC2A 3PX, England, United Kingdom*

Cerebral metastases usually produce distressing symptoms and an early death. It is not known which groups of patients are most at risk from developing this complication nor its optimal treatment. Radiotherapy is the treatment used most often but although prolonged responses are occasionally seen, it often fails to palliate symptoms and may cause considerable disturbance to the patient. Forty-two cases of cerebral metastases have been studied to analyze the results of treatment and the relevance of certain prognostic variables.

233. PALLIATION OF BREAST CANCER BY LEVODOPA (HUMAN)

Fletcher, W. S., Oregon State Higher Education System, University of Oregon Health Sciences Center, School of Medicine, Dept. of Surgery, *3181 S.W. Sam Jackson Park Rd., Portland, Oregon*, 97201, United States of America

This is part of a broader project. A summary of this subproject is not available.

234. NAFOXIDINE OR TAMOXIFEN FOR PALLIATION OF METASTATIC BREAST CANCER

Fletcher, W. S., Oregon State Higher Education System, University of Oregon Health Sciences Center, School of Medicine, Dept. of Surgery, *3181 S.W. Sam Jackson Park Rd., Portland, Oregon*, 97201, United States of America

This is part of a broader project. A summary of this subproject is not available.

235. INSTILLATION OF ETHANOL INTO THE PITUITARY TO RELIEVE CANCER PAIN

Takeda, F., Fujii, T., Tozawa, R., Saitama Cancer Center, Neurosrgery & Anesthesiology Clinic, *818 Komoro, Ina-Machi, Kitaadachi-Gun, Saitama-Ken 362, Japan*

OBJECTIVE: 1) Intractable pain due to cancer metastases should be reasonably alleviated through a safe and long-acting therapeutic procedure, chemical hypophysectomy, without causing uncontrollable side effects. 2) The mechanism through which the chemical ablation of the pituitary relieves the cancer pain should be elucidated. 3) Diabetes insipidus, the most hazardous side effect of the hypophysectomy, should be safely managed.

APPROACH: 1) The procedure is instillation of ethanol into the pituitary through transnasal puncture of the sella turcica essentially in accordance to Moricca's method. 2) Endocrinological evaluation of the pituitary function should be done before and after the treatment. 3) Pathological examination should be done if possible.

PROGRESS: 1) The instillation of ethanol into the pituitary was performed 50 times on 37 patients with minimum complications. Excellent pain relief was obtained almost instantaneously in all of the cases, and persisted for a long period up to 15 months. 2) An excellent and long-lasting pain relief could be obtained with sufficient inactivation of the anterior and posterior pituitary functions, and pain relief without sufficient pituitary inactivation might be temporary or incomplete. 3) One curious fact was observed: ACTH and endorphin in serum and cerebrospinal fluid were significantly elevated at the post-treatment stage. These changes in lipotropin-related peptides might offer a clue to the mechanism of cancer pain relief which would be mediated through central nervous system. 4) Indomethacine prevented or reduced the polyuria which occurred in the early post-treatment stage, and rendered an easy management of water-electrolyte balance. 5) In autopsy cases, there was a widespread necrosis in the pituitary gland, but routine histological examinations failed to reveal any morphological alteration in the hypothalamus.

236. PARATHYROID ALLOTRANSPLANTATION AS PALLIATIVE THERAPY

Geis, W. P., Paloyan, E., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Transplantation Section, *5th Ave. & Roosevelt Rd., Hines, Illinois*, 60141, United States of America

No further activity in this program since last report. There have been no patients with parathyroid insufficiency who require parathyroid transplantation. The solitary recipient continues to have normal parathyroid function along with normal serum calcium and phosphorus.

237. PROLACTIN SUPPRESSION FOR BONE PAIN FROM METASTATIC BONE CANCER (HUMAN)

Malarkey, W. B., Ohio State University, Columbus Campus, School of Medicine, Dept. of Medicine, *370 W. 9th Ave., Columbus, Ohio*, 43212, United States of America

This is part of a broader project. A summary of this subproject is not available.

238. DELTA-9-THC AND COMPAZINE IN CANCER CHEMOTHERAPY

Ungerleider, J. T., University of California, Los Angeles Campus, School of Medicine, Dept. of Surgery, *2025 Zonal Ave., Los Angeles, California*, 90024, United States of America

The purpose of this study is to compare the effectiveness of delta-9-THC and prochlorperazine (Compazine) in controlling the nausea, vomiting, and loss of appetite frequently associated with cancer chemotherapy. Candidates for this study will be cancer inpatients and outpatients currently being cared for in the UCLA Departments of Medical and Surgical Oncology. Subjects will be of adult age and English speaking, not mentally disabled or pregnant. Approval will be obtained from the UCLA Human Subject Protection Committee and informed consent -from the patient. Drugs will be dispensed in double-blind fashion according to one of two randomly chosen schedules. Medication is to be taken orally every 4 hours for 4 doses, beginning 1/2 hour before chemotherapy initiation. One of the 4 doses will be taken in the clinic and 3 at home. Unused medication will be returned to the pharmacy and careful records kept. Patients and the staff will estimate degree and duration of nausea and vomiting, as well as appetite and food intake. Mental status for mood will be assessed pre- and post-drug administration by patients and, in some cases, by a brief pre-chemotherapy psychiatric interview. Approximately 400 chemotherapy cycles will be included in this study, requiring the participation of approximately 200 patients.

239. EVALUATION OF 9-THC AS AN ANTIEMETIC IN PATIENTS WITH MALIGNANCIES UNDERGOING CHEMOTHERAPY

Fuks, J. Z., Wiernik, P. H., Aisner, J., Schnaper, N., Bachur, N., Egorin, M. J., Brenner, D., Riggs, C., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Section of Medical Oncology, *Baltimore, Maryland*, 21201, United States of America

Nausea and vomiting are frequent and distressing side effects of cancer chemotherapy and the severity of these symptoms contributes to the decreased ability of patients to undergo long-term chemotherapy. The phenothiazines have marginal value for nausea and vomiting and more effective antiemetic therapy is needed. THC has recently been identified to contain significant antiemetic potential. This randomized, double-blind, placebo controlled study compares the antiemetic effectiveness of 9THC with a standard phenothiazine antiemetic, prochlorperazine. Furthermore, since THC can induce tolerance to THC this study also examines whether 9THC alters drug handling of the chemotherapeutic agents.

240. MARIJUANA AND CANCER PATIENTS

Saiers, J. H., Kellner, R., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology & Oncology Section, *2100 Ridgecrest Dr. S.E., Albuquerque, New Mexico*, 87108, United States of America

OBJECTIVE: To evaluate the efficacy of oral versus inhaled tetrahydrocannabinol (THC) in alleviating nausea and vomiting due to cancer chemotherapy; also, to determine if tolerance occurs to repeated doses of oral inhaled THC, determined by its effect on nausea and vomiting due to cancer chemotherapy.

BACKGROUND: Physicians have been confronted with numerous anecdotal reports of patients concerning the effect of marijuana in relieving the nausea and vomiting of cancer chemotherapy. There have been several controlled studies of short duration providing evidence supportive of these narrative accounts. Patients have also reported that tolerance to the antiemetic effect of marijuana does occur. The present study is designed to test this hypothesis as well as to determine whether THC is more effective orally or by inhalation. Patients who desire to enter the program will be screened by a board and if accepted will receive marijuana, either by capsule or by inhalation.

241. EFFECT OF NABILONE ON NAUSEA AND VOMITING OF CANCER CHEMOTHERAPY

EinHorn, L. H., Indiana University, Indiana University - Purdue University at Indianapolis, School of Medicine, Dept. of Medicine, *1219 W. Michigan St., Indianapolis, Indiana*, 46202, United States of America

This is part of a broader project. A summary of this subproject is not available.

242. AN EVALUATION OF THE ANTIEMETIC EFFECT OF NABILONE IN CANCER PATIENTS

Herman, T. S., Jones, S. E., Bressler, R., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology/Oncology Section, *3601 S. 6th St., Tucson, Arizona*, 85723, United States of America

Two double-blind, crossover trials comparing the antiemetic effectiveness of nabilone, a new synthetic cannabinoid, with that of prochlorperazine were conducted in patients with severe nausea and vomiting associated with anticancer chemotherapy. Of 113 patients evaluated, 90 (80 per cent) responded to nabilone therapy, whereas only 36 (32 per cent) responded to prochlorperazine (p less than 0.001). Complete relief of symptoms was infrequent, occurring only in nine patients (8 per cent) given nabilone. When both drugs were compared, both nausea (p less than 0.01) and vomiting episodes (p less than 0.001) were significantly lower in patients given nabilone. Moreover, patients clearly favored nabilone for continued use (p less than 0.001). Predominant side effects noted by patients were similar for both agents and included somnolence, dry mouth and dizziness but were about twice as frequent and more often severe in patients receiving nabilone. In addition, four patients (3 per cent) taking nabilone had side effects (hallucinations in three, hypotension in one) that required medical attention. Euphoria associated with nabilone was infrequent (16 per cent) and mild. (N. Engl. J. Med. 300: 1295-1297, 1979).

Further research with nabilone has been discontinued because of the finding of toxicity in dogs. If these results are found not to be applicable to human treatment, then we will try to determine the optimal dose of nabilone to maximize the therapeutic benefit in relationship to toxicity. Estimated timing is one year.

243. OMRF 79-01 - EVALUATION OF TIGAN CAPSULES IN THE TREATMENT OF NAUSEA AND VOMITING ASSOCIATED WITH CANCER CHEMOTHERAPY

Bottomley, R. H., Hussein, K. K., Murray, J. L., Grozea, P. N., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Hematology Section, *921 N.E. 13th St., Oklahoma City, Oklahoma*, 73104, United States of America

The purpose of this study is to compare the efficacy of Tigan capsules with placebo capsules in the treatment of nausea and vomiting associated with cancer chemotherapy.

Patients with cancer undergoing chemotherapy are eligible for this study, specifically patients receiving drugs that are known to be associated with nausea and vomiting such as nitrogen mustard (alone and in combination with other chemotherapeutic agents), DTIC, adriamycin, actinomycin-D and other agents known to cause vomiting.

The experimental design is to administer either Tigan 500 mg (two 250 mg capsules or two placebo capsules) at the time the patient becomes nauseated after receiving chemotherapy. Doses will be repeated every five hours for four doses. If uncontrollable vomiting occurs then other alternatives can be used and the patient will be taken off the protocol.

This study is continuing with no changes in the protocol.

244. ANTIEMESIS IN CANCER CHEMOTHERAPY WITH METOCLOPRAMIDE

Wampler, G. L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Oncology Section, *1201 Broad Rock Rd., Richmond, Virginia*, 23249, United States of America

PROJECT OBJECTIVE: To determine the efficacy of 6 mg/kg/day of injectable metoclopramide (Reglan) in the prevention of vomiting in patients undergoing cancer chemotherapy.

PLAN: Treatment using metoclopramide as the antiemetic in 10 patients being treated with cisplatinum.

METHOD: Number of vomiting episodes will be monitored.

CLINICAL RELATIONSHIP: This is a clinical study attempting to develop better antiemetics for cancer chemotherapy.

245. COMBINATION ANTIEMETIC THERAPY FOR CANCER CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Kuhn, J. G., Pollard, E. B., Von Hoff, D. D., Barnett, T., Clark, G., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *San Antonio, Texas*, 78284, United States of America

The proposed project will evaluate the effectiveness of a combination antiemetic regimen as compared to standard therapy and to a placebo in the prevention of nausea and vomiting associated with the administration of cisplatinum. The study will be a randomized double-blind study. Thirty-six patients will act as their own controls and each will be given one course of each of the following: Torecan/Valium, Torecan/placebo and Valium/placebo, in a randomized fashion. The patients will be treated during three consecutive courses of cisplatinum containing regimens.

This will be the first study utilizing the combination of Torecan/Valium for the prevention of nausea and vomiting associated with the administration of cisplatinum. If the combination regimen is shown to be efficacious, this practice could relieve a major side effect of the treatment.

246. REDUCING ADVERSE REACTIONS TO CANCER CHEMOTHERAPY

Burish, T. G., Vanderbilt University, School of Arts & Sciences, Dept. of Psychology, *21st Ave. S., Nashville, Tennessee*, 37232, United States of America

The proposed research investigates the effectiveness of behavioral procedures in reducing the conditioned aversive responses developed by many cancer patients to their chemotherapy treatment. The initial series of studies will assess the effectiveness of skin temperature biofeedback, EMG biofeedback, and progressive muscle relaxation training in reducing the conditioned nausea, vomiting, physiological arousal, and negative affect displayed by veteran chemotherapy patients. A subsequent investigation will assess the effectiveness of the most successful behavioral procedure, as indicated by the initial series of studies, in preventing and ameliorating the development of conditioned adverse responses in new chemotherapy patients. A third area of investigation will involve exploring the effectiveness of behavioral treatment versus drug treatment (anti-emetic/anti-anxiety medication), and a combination of behavioral treatment and drug treatment versus either treatment alone, in reducing the distress of cancer patients undergoing chemotherapy. Finally, a retrospective investigation will be carried out to identify psychosocial and demographic variables which may characterize cancer chemotherapy patients and which may have prognostic value in determining which types of patients will profit from receiving biofeedback and/or progressive muscle relaxation procedures.

247. NERVE FASCICLE LIGATION AND NEUROMA FORMATION

Battista, A. F., Cravioto, H. M., New York University, School of Medicine, Dept. of Neurosurgery, *550 1st Ave., New York, New York*, 10016, United States of America

Fascicle ligation for neuroma pain in 8 patients has produced relief of pain in all cases since operation: 43 mths (in 2 patients), 41 mths, 33 mths, 20 mths, 14 mths, 10 mths and 9 mths. Light and EM studies of human painful and non-painful amputation neuromas continue to support the observation of more unmyelinated axons in painful than in non-painful neuromas. Neuroma formation in rats, cats and monkeys has shown grossly a markedly decreased bulk in the neuromal area of nerves sectioned, doubly ligated, and careful cauterization as compared to neuromas formed after cutting with or without whole nerve ligation. Light and EM studies indicate a paucity of axons in the area of the fascicle ligation and cauterization as compared to the number in the neuroma formed after nerve cutting with or without whole nerve ligation. Evidence indicates that by preventing rupture of the perineurium axons are thereby contained which limits neuroma formation and maintains an orderly arrangement of nerve fiber bundles.

248. TRANSCUTANEOUS NEURAL STIMULATION IN CANCER PAIN

Rosomoff, H. L., University of Miami, School of Medicine, Dept. of Oncology, *1400 N.W. 10th Ave., Box 520875, Coral Gables, Florida*, 33152, United States of America

This is part of a broader project. A summary of this subproject is not available.

249. EVALUATION AND CONTROL OF CHRONIC PAIN IN CANCER

Wolff, B. B., Kantor, T. G., Battista, A. F., Rubin, M., Lewis, L. R., Feldman, N., New York University, School of Medicine, Dept. of Psychiatry, *550 1st Ave., New York, New York*, 10016, United States of America

The objective is to evaluate four pain-relieving treatment categories for persistent chronic pain in cancer to yield optimal pain control methods for a patient with minimal drug dosage to allow maximal benefit and optimal psychosocial functioning. Adult cancer patients with persistent chronic pain, even after establishment of a plateau with chemotherapy, will be referred by their physicians to the multi-disciplinary Pain Group for specific evaluation, and management of pain. This will involve physical (medical and/or dental) examination, psychological interview and tests; social interview with patient and family; and laboratory pain-induction methods (i.e., controlled and standardized electrical, thermal, chemical and mechanical stimulation to elicit the pain threshold and tolerance levels). Baseline drug requirements will then be established per patient and maintained throughout the investigation. Then each patient will be assigned randomly to one of four therapeutic categories, namely 1) baseline plus analgesic drugs; 2) baseline plus transcutaneous electrical nerve stimulation; 3) baseline plus acupuncture; and 4) baseline plus psychotherapy for 2-4 weeks and then crossover to another modality. Preliminary work indicated combination of two modalities to be more effective than single therapy. Patient will be offered treatments most beneficial to him.

Paid, adult healthy volunteers will be subjects of a study using these laboratory pain-induction methods and treatment modalities in a complete crossover balanced but randomized design to evaluate efficacy of each therapy in regard to experimental pain. Our previous work demonstrated that our standard pain tests can discriminate analgesic therapeutic modalities significantly from placebo, but only single modalities were used. This project proposes to study the effects of combined modalities on experimental pain. Ultimately, these studies should yield more information on behavioral mechanisms of analgesic treatment modalities.

250. CANCER PAIN MANAGEMENT - BROMPTON MIXTURE AS A MODEL

McDonald, R. H., Klaniecki, T. S., Neil, J. F., Blair, C., University of Pittsburgh, School of Medicine, Dept. of Medicine, *3550 Terrace St., Pittsburgh, Pennsylvania*, 15261, United States of America

The Brompton Mixture is a relatively new approach to narcotic analgesic therapy, especially in the United States. The mixture consists of an elixir containing a narcotic (usually morphine), cocaine, ethyl alcohol, cherry syrup and water. A phenothiazine is usually given with the mixture.

Early studies have suggested that the Brompton Mixture offers significant advantages over conventional narcotic therapy in that (1) pain is significantly reduced by relatively low doses of oral narcotics, (2) significant tolerance does not appear to develop even after years of treatment and (3) adequate levels of analgesic can be induced without serious side effects. However, there have been no controlled studies designed to determine whether the Brompton Mixture is significantly more effective than narcotic alone, and if so, which component of the mixture is responsible for the enhanced effectiveness.

Two other significant aspects of the study are (1) its use of a series of psychological tests to assess mood changes in concert with pain relief, and (2) its use of a computer based decision

tree to modify medication doses, allowing a double-blinded state to be maintained during the study.

251. USE OF SELF-HYPNOSIS FOR CONTROL OF PAIN

Zeltzer, L. K., Barbour, J. S., Zeltzer, P. M., Kalmowitz, J. A., Geiser, C., LeBaron, S., University of Texas, Health Science Center at San Antonio, Medical School, Dept. of Pediatrics, *7703 Floyd Curl Dr., San Antonio, Texas*, 78284, United States of America

This study will evaluate the effectiveness of self-hypnosis for control of pain, nausea, and vomiting in adolescents with cancer. Adolescents, ages 12-21 years, treated at the Children's Cancer Center and experiencing any of the above problems are offered entry into the study. Experimental subjects are trained in the use of self-hypnosis, while control subjects receive supportive counseling. All subjects are pre-tested and followed up at 6 months and 1 year on tests of trait anxiety, self-esteem, health locus of control, and impact of illness and treatment. They also are given a belief system questionnaire, while their families are interviewed in their homes. In addition, during a baseline period and the 1 year intervention period, patients are monitored with structured self-reports of (1) anxiety and discomfort associated with procedures (IV's, bone marrows, spinal taps), (2) nausea and vomiting associated with chemotherapy, (3) chronic pain associated with disease, and (4) amounts and frequency of analgesics, antiemetics, or tranquilizers. A chart review summarizes hospitalization, medications, disease course, and compliance with procedures, chemotherapy, and clinic visits.

Pilot data on 11 adolescents using hypnosis for procedures and chemotherapy demonstrated significant reductions in pain, anxiety, nausea, and vomiting. This controlled study will determine whether the hypnosis or increased patient contact is responsible for these changes and how consistent and persistent these changes are. The study will also examine how decreasing symptomatology affects patient compliance.

252. PILOT STUDY OF PAIN IN FOUR SELECTED CANCERS

Bonica, J. J., Hutchinson, W. B., Perrin, E. B., Benedetti, C., Bergner, M., University of Washington, School of Medicine, Dept. of Anesthesiology, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington*, 98195, United States of America

The primary goal or objective of this pilot study is to help define the incidence, prevalence, and magnitude of pain associated with cancer and its impact on the patient and the family. This is to be achieved by developing and testing a methodology to determine (1) the pain associated with cancer of the lung, pancreas, uterine corpus and prostate; (2) the time during the course of the disease when pain occurs; (3) the subsequent course of pain, including its intensity, quality, periodicity, site, subsequent spread, duration and other characteristics; and (4) the relationship between pain and various psychological and social factors affecting the patient.

The research will be conducted using a population-based cancer registry to estimate the incidence and prevalence of pain by stage of disease for each of the four cancers. Comparison will be made of incidence and prevalance rates ascertained both cross-sectionally and longitudinally. Measures of pain developed for the project will be tested for reliability and validity. The results of this research will have implications for further collaborative efforts using population-based cancer registries to study the natural history and impact of cancer pain. The research will also provide data necessary for planning of pain management programs.

253. A PILOT STUDY OF CANCER PAIN

Cleeland, C. S., Crowley, J. J., Schwettmann, R. S., Daut, R. L., Reinhardt, L., University of Wisconsin, Madison Campus, Medical School, Dept. of Neurology, *450 N. Randall Ave., Madison, Wisconsin*, 53706, United States of America

This project will be composed of a series of studies which are prerequisite to the description of the course and natural history of pain in cancer. The objectives are to: (1) develop measuring instruments which are sensitive to the presence of pain in patients with cancer, and when pain is present, measure its intensity and impact on the patient, (2) develop and pilot a method of classifying the physical basis of pain experienced by the patient with cancer and determine the most efficient method by which this classfication can be made, (3) conduct a cross-sectional study of pain using the instruments developed in a sample of patients with cancer at 4 sites and at 3 stages of progression, and (4) determine the attitudes towards pain, its treatment, and its relation to the progression of the disease maintained by those responsible for the treatment of cancer. In order to accomplish the goals of the study, a research team will be established which will include persons whose background will allow for completion of each of the objectives. Four sites of cancer (breast, colon-rectal, gynecological, and prostate) will be selected for study because of their high incidence, both in the general population and in our institution.

Information will be collected according to a timetable which will allow for a series of reports concerning each of the objectives which should be of use to other investigators of this problem and which should lead to a feasibility study for the conduct of a large-scale collaborative study of pain in cancer.

254. PAIN AND ANXIETY IN CHILDREN WITH ACUTE LEUKEMIA

Kellerman, J., Children's Hospital of Los Angeles, Dept. of Pediatrics, *4650 Sunset Blvd., Los Angeles, California*, 90054, United States of America

This study was designed to evaluate the efficacy of training in hypnosis in reducing pain and anxiety in children with acute lymphoblastic leukemia (ALL) undergoing bone marrow aspirations (BMA's). Patients/subjects were selected from the population of children between the ages of 6 and 10 years of age with ALL, receiving outpatient treatment in the Division of Hematology-Oncology at Children's Hospital of Los Angeles. The design calls for randomization of 40 patients to either hypnosis or attention/placebo groups, with stratification of the sample by sex. Baseline measures are collected along four dimensions: behavioral observation, nurse ratings, and structured self-ratings of pain and anxiety. Two training sessions are offered post-baseline and prior to the next outpatient bone marrow aspiration. Further sessions are provided prior to each of three post-baseline bone marrow aspirations and response to training is monitored using the four dependent measures. Seventeen patients accrued to the study in Year 1, 9 in the hypnosis group, 8 in the comparison group. Baseline data was collected on all patients. Fourteen of 17 patients have completed 2 sessions of introductory training (7 each in both hypnosis and comparison groups). Twelve patients have undergone at least one post-training bone marrow aspiration (6 each in both groups). Of these, 4 patients (three patients in the hypnosis group and one patient in comparison group) have undergone 2 BMA's, and 2 patients (one each, in both groups) have completed the study protocol and have gone off-study (three post-training BMA's). Two methodological modifications were made. Hypnotic susceptibility testing was not done because the major pediatric susceptibility scales were, essentially, hypnotic inductions. Exposing comparison group patients to hypnotic induction would have confounded the controlled nature of the study. A quantified rating of the child's response to either hypnosis or the attention/placebo dimension was added as a factor to be correlated with treatment efficacy. All data were coded prospectively.

255. THE PREVENTION OF SHAKING CHILLS AND FEVER WITH INTRAVENOUS MEPERIDINE OR HYDROCORTISONE

Finley, R., Aisner, J., Fortner, C. L., Wiernik, P. H., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Clinical Research Pharmacy Section, *Baltimore, Maryland*, 21201, United States of America

The objective of this study is to evaluate and compare the efficacies of intravenous meperidine and hydrocortisone in preventing shaking chills associated with amphotericin therapy. Patients are randomized to receive either meperidine or hydrocortisone by IV push prior to the infusion, or as an addition to the infusion. The occurrence of shaking chills and time interval between the beginning of the amphotericin infusion and the chills are being evaluated.

256. A STUDY OF REGISTERED NURSES' ATTITUDES TOWARDS PAIN IN THE CANCER PATIENT

Brady, I. D., Summers, S., Lehman, R., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, *921 N.E. 13th St., Oklahoma City, Oklahoma,* 73104, United States of America

An important everyday aspect of the clinical nurse's practice is caring for patients in pain and alleviating their suffering. The nurse's response in this situation depends upon a number of factors including inferences drawn from observation of the patient and the belief and attitudes acquired about suffering which influence the nurse's behavior. Pain threatens the quality of life of the cancer patient and he is uncertain when and if he will receive pain medication when he requests it.

Our collective years of contacts with registered nurses have impressed us with their reactions and comments as they cared for cancer patients; they often verbalized doubts about the patient's pain. We asked why some nurses reacted to cancer patients this way and wondered if they were aware of their attitudes. Our interactions with cancer patients in pain have indicated that they are aware of the nurses' reactions and that some have felt the nurse did not understand their suffering.

This will be an exploratory study using the general form of the semantic differential to determine registered nurses' attitudes regarding pain in cancer patients. Factors scores will be analyzed to describe the grouped data employing statistical measures of mean, standard deviation and frequency distributions. Distance cluster analysis will be utilized to measure the distance between concepts.

257. COMBINED ADMINISTRATION OF PENTAZOCINE AND MORPHINE (HUMAN)

Houde, R. W., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

258. RELATIVE ORAL-PARENTERAL POTENCY OF PROPIRAM FUMARATE IN CHRONIC PAIN

Houde, R. W., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

259. ANALGESIC POTENCY OF TILIDINE AND MORPHINE (HUMAN)

Houde, R. W., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

260. ANALGESIC POTENCY OF ORAL SU-19713B AND CODEINE (HUMAN)

Houde, R. W., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

261. POTENCY OF ANALGESICS IN CANCER PATIENTS

Houde, R. W., Sloan Kettering Inst. for Cancer Research, *410 E. 68th St., New York, New York,* 10021, United States of America

This is part of a broader project. A summary of this subproject is not available.

262. MOLECULAR MECHANISMS OF ANALGESIA

Pasternak, G. W., Memorial Sloan Kettering Cancer Center, Neuro-Oncology Laboratory, *1275 York Ave., New York, New York,* 10021, United States of America

No summary has been provided to the Smithsonian Science Information Exchange.

263. CONTROL OF PAIN IN CANCER

Nashold, B. S., Duke University, School of Medicine, Dept. of Medicine, *Box 3711, Durham, North Carolina,* 27710, United States of America

This is part of a broader project. A summary of this subproject is not available.

264. PAIN CONTROL IN CANCER PATIENTS

Kirsch, W. M., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Neurosurgery, *4200 E. 9th Ave., Denver, Colorado,* 80262, United States of America

We will continue to be in contact with our consultant, Dr. John Swett, and recordings from peripheral nerves will be continued on our panel of patients.

In addition, experiments are planned in which the peripheral nerve studies will be repeated in anesthetized dogs using the same devices that are implanted in humans.

265. PAIN CONTROL IN CANCER

Addison, R. A., Rehabilitation Inst. of Chicago, *345 E. Superior St., Chicago, Illinois,* 60611, United States of America

OBJECTIVE: Study and evaluate various methods of controlling pain in cancer treatments.

266. PAIN CONTROL IN CANCER

Bennett, M., University Hospital Inc., *75 E. Newton St., Boston, Massachusetts,* 02118, United States of America

OBJECTIVE: Study and evaluate various methods of controlling pain in cancer patients.

267. PAIN CONTROL IN CANCER

Ignelzi, R. J., University of California, San Diego Campus, School of Medicine, Dept. of Surgery, *P.O. Box 109, La Jolla, California,* 92093, United States of America

OBJECTIVE: Study and evaluate various methods of controlling pain in cancer patients.

268. PAIN CONTROL IN CANCER

Margolis, C., Thomas Jefferson University, Jefferson Medical College, Dept. of Psychiatry & Human Behavior, *1025 Walnut St., Philadelphia, Pennsylvania,* 19107, United States of America

OBJECTIVE: Study and evaluate various methods of controlling pain in cancer patients.

269. PAIN CONTROL IN CANCER

Bonica, J. J., University of Washington, School of Medicine, Dept. of Anesthesiology, *A-300 Health Sciences Ctr., SC-64, Seattle, Washington,* 98195, United States of America

OBJECTIVE: Study and evaluate various methods of controlling pain in cancer treatments.

270. PAIN CONTROL IN CANCER

Duncalf, D., Montefiore Hospital & Medical Center, *111 E. 210th St., Bronx, New York.* 10467, United States of America

OBJECTIVE: Study and evaluate various methods of controlling pain in cancer patients.

271. PAIN CONTROL IN CANCER

Schwettmann, R. S., University of Wisconsin, Madison Campus, Medical School, Dept. of Anesthesiology, *450 N. Randall Ave., Madison, Wisconsin,* 53706, United States of America

OBJECTIVE: Study and evaluate various methods of controlling pain in cancer treatments.

272. SOUTHEASTERN CANCER STUDY GROUP

Philpott, G. W., Sufrin, G., Wallack, M., Loeb, V., Stewart, C., Perez, C., Wasserman, T., Ratkin, G., Valeriote, F., Washington University, School of Medicine, Dept. of Surgery, *660 S. Euclid Ave., St. Louis, Missouri,* 63110, United States of America

Washington University School of Medicine will participate in studies of the Southeastern Cancer Study Group, which will be described in detail in the Headquarters grant application from the University of Alabama. Briefly, these are cooperative, interdisciplinary, clinical cancer studies, utilizing chemotherapy, surgery, radiotherapy, immunotherapy and combination of these modalities. Phase I, II, III and adjuvant studies are proposed for consenting patients with cancer, predominantly adults with solid tumors. The methods used will be those approved for cooperative group studies, and will include standard techniques of diagnosis, treatment, laboratory studies and data processing used in solid tumor management. The cumulative data base devised from these studies is expected to aid in predicting the results of conventional therapy for the tumors studied in the participating institutions. In addition, the relatively new approach of treating

cancer patients with high dose chemotherapy and irradiation followed by autologous bone marrow transplantation will be studied in collaboration with several of the SECSG institutions. The ultimate goal of all of this research is to improve the longevity and increase the palliation of adults with solid tumors.

273. ANTICANCER VOMITING - DELINEATION AND CONTROL

McCarthy, L. E., Borison, H. L., Ware, P. A., Dartmouth College, Dartmouth Medical School, Dept. of Pharmacology & Toxicology, *P.O. Box 833, Hanover, New Hampshire,* 03755, United States of America

An animal model is proposed for the objective quantification of vomiting induced by anticancer agents, and for testing new classes of antiemetics against these drugs. Recording of intrathoracic pressure via a jugular venous catheter provides a continuous monitor of emetic activity in unrestrained awake cats. Emesis produces a unique and unambiguous sequence of pressure variations in the thoracic cavity which distinguishes two basic emetic components, namely retching and expulsion. Cumulative vomiting episodes plotted against time establish a characteristic emetic response profile for each drug. Three anticancer agents (BCNU, mechlorethamine and cis-Pt) will be defined in this way, as will selected standard emetic drugs (deslanoside, apomorphine and veratrum). The antiemetic action of certain psychoactive compounds, i.e., nabilone (a synthetic cannabinoid), three narcotics (morphine, Fentanyl and methadone) and prochlorperazine will be assessed on the basis of their effect on the standard emetic response profile of each of the emetic agents. Specific end-points for determining antiemetic activity include latency, severity and time course. Development of tolerance to the various agents after repeated exposure will be evaluated. Additionally, neurophysiological experiments are devised for elucidating locus and mechanism of drug action if time permits.

274. NATURAL HISTORY OF LYMPHOSARCOMA AND ROLE OF RADIAL AND PALLIATIVE THERAPY

Prosnitz, L., Yale University, School of Medicine, Dept. of Therapeutic Radiology, *333 Cedar St., New Haven, Connecticut,* 06510, United States of America

This is part of a broader project. A summary of this subproject is not available.

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6) GIVE MONTH AND YEAR FOR END OF CURRENT FUNDING

7) DESCRIBE PROJECT UNDER THREE HEADINGS: 1) OBJECTIVE; 2) APPROACH; AND 3) PROGRESS [optional] (use specific, technical terms)

PLEASE CHECK ONE: _____ **1. This is a description of a NEW Project.**

_____ **2. This is a REVISED description of Project No.** _____
(Insert identification number)

FORM APPROVED: OMB NO. 068-R1441 EXP. AUG. 1983

CANCER RESEARCH REGISTRY

A Service of the National Cancer Institute

INTERNATIONAL CANCER RESEARCH DATA BANK (ICRDB) PROGRAM

You are invited to complete a Current Cancer Research Project Registration Form PROVIDED you have NOT completed a similar form for the Smithsonian Science Information Exchange (SSIE), the Clearinghouse for Ongoing Research in Cancer Epidemiology in Lyon, France, or for the Current Cancer Research Project Analysis Center (CCRESPAC) during the last eight months.

Your project description will be entered into the National Cancer Institute's (NCI) data base, CANCERPROJ (**Cancer Proj**ects). Your project description will also appear in one or more of the ICRDB publications known as SPECIAL LISTINGs of Current Cancer Research. Every year the ICRDB publishes fifty SPECIAL LISTINGs, each containing project descriptions in different specific oncology research areas. A free copy of a SPECIAL LISTING is automatically sent to each investigator whose project description appears in that SPECIAL LISTING. Thus, investigators are annually made aware of research being carried out in their areas of interest.

GUIDELINES FOR FILLING OUT THE REGISTRY FORM

A. The description should be submitted by or through the individual who is the **principal investigator** of the project described. Major co-investigators should also be listed.

B. If you are working on more than one project, or if your one project consists of several distinct major segments, please prepare a separate summary form for each.

C. Only **CANCER** research projects which are CURRENTLY **ACTIVE** and CURRENTLY **FUNDED** should be submitted.

D. If you are submitting a clinical protocol, please send a copy of the complete protocol. The NCI has an established format which will be used to develop a standard protocol summary. A copy of the prepared summary will be sent to you for review prior to its entry into the data base.

E. Return to address shown on the front of this form.

F. IMPORTANT. If you prefer to have your copy of the SPECIAL LISTING mailed to your home address, or if your co-investigators have different mailing addresses, please list each name and address on a separate sheet of paper.

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